Cost-effectiveness Analysis of Hygiene-based Strategies Aimed toward Prevention of SSTI and MRSA-Associated SSTI among U.S. Active Duty Army Trainees

by

Stephanie M. Morrison

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Name of Candidate: Stephanie M. Morrison
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DISSERTATION AND ABSTRACT APPROVED:

DATE:

25 Mar 15

Dr. Dechang Chen
DEPARTMENT OF PREVENTIVE MEDICINE AND BIOMETRICS
Committee Chairperson

25 MAR 15

Dr. David R. Tribble
DEPARTMENT OF PREVENTIVE MEDICINE AND BIOMETRICS
Dissertation Advisor

25 MAR 15

Dr. Michael W. Ellis
DEPARTMENT OF MEDICINE
Committee Member

Katherine Anderson Bradbury 25 Mar 15

Dr. Katherine Anderson Bradbury
ASSISTANT PROFESSOR, LINCOLN MEMORIAL UNIVERSITY
Committee Member

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DEDICATION

To my husband, my rock, without your laughter, supportive ear, and belief in me and my work, I would not have made it to the summit of this milestone.

To my late father, thanks for believing in me and pushing me to be the very best of myself. The many early struggles were worth it.

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Stephanie M. Morrison

May 15,2015

ABSTRACT

Cost-effectiveness Analysis of Hygiene-based Strategies Aimed toward Prevention of SSTI and MRSA Associated SSTI among U.S. Active Duty Army Trainees

Stephanie M. Morrison, Doctor of Public Health, 2015

Thesis directed by: David R. Tribble M.D., Dr.P.H., Professor, Preventive Medicine and Biometrics Department

Since the early 2000's, skin and soft tissue infections (SSTI) with *Staphylococcus aureus* (*S.aureus*) involvement have been an important public health problem within the recruit training population. The burden of these infections has been evaluated in clinical terms, but less is understood with respect to the time and costs associated with these infections. Multiple MRSA SSTI outbreaks occurred and a number of recommendations were made regarding the prevention and interruption of transmission of these infections among trainees. These recommendations included hygiene strategies such as regular hand washing and showering (sometimes with an agent such as chlorhexidine), implementing a hygiene education program, and disinfecting surfaces potentially contaminated with the *S.aureus* organism. The results regarding the effectiveness of these hygiene strategies within the military training setting have been mixed. A gap in knowledge existed with respect to not only the cost of these programs, but the effectiveness in terms of its effect on lost time in training. This study's purpose was to evaluate the burden of overall,

S.aureus and MRSA SSTI in terms of time and costs and then identify cost effective approaches for reducing this burden.

Military health systems datasets were used to retrospectively evaluate lost-time in training and cost burden of overall, *S.aureus* and MRSA SSTI. ICD-9-CM codes were used to identify skin and soft tissue infections, these codes were then linked with clinical microbiology information to identify *S.aureus* and MRSA SSTI. Lost time in training was calculated as the sum of time spent away from training due to clinic or hospital visits as well as convalescence and training remediation. Cost of illness was equivalent to the sum of direct medical costs (costs associated with medical care such as office visits, laboratory procedures, and prescriptions) and indirect costs (costs associated with lost work productivity because of illness). A systematic review of the literature was performed to determine the effects of hand and personal hygiene programs aimed toward acute infections like SSTI in terms of risk reduction. Additionally, the cost effectiveness of hygiene strategies aimed toward overall and MRSA SSTI among recruit trainees was evaluated using information obtained from a prospective trial implemented at Fort Benning, Georgia. A decision analysis framework was constructed and cost effectiveness was computed using the costs averted and time averted when using a certain strategy compared to standard practice along the infection pathway.

Results showed that the burden of illness in terms of time and cost were substantial across the five Army training facilities during the four year study period from 2006 through 2009. Annual rates of overall, *S.aureus* and MRSA SSTI ranged from 197-218, 132-151, and 86-99 per 100 training cycles, respectively. Trainees lost approximately 18,000 days annually, of which approximately 4500 days (25%) were due

to training remediation. SSTI overall cost approximately $12 million USD per year across all five training sites. Indirect costs comprised 80% of the total costs (~$10 million USD per year). Rates, time, and costs were all highest during phase one of training. Complicated infections contributed to increased rates, lost time in training, and costs. Increased lost time and costs was observed among those trainees with an overall SSTI who were cultured positive for MRSA, received an I&D procedure and prescribed an antibiotic regimen that covered for MRSA.

A systematic review and meta-analysis of the literature revealed that hand and personal hygiene promotions programs had a beneficial effect toward acute communicable infections like gastrointestinal, respiratory, and skin infections. Further analysis revealed that significant heterogeneity existed around the pooled risk ratios, the source of which was not identified. Although a chlorhexidine strategy with a hygiene component was shown to be protective against SSTI within the community, results should be viewed with caution. The studies used to generate this pooled estimate were observational-analytic by nature and inherent to bias; therefore, the results could be spurious.

A cost effectiveness analysis was performed to evaluate the cost effectiveness of hygiene strategies (standard, enhanced standard, and chlorhexidine) implemented during a prospective trial at Fort Benning, Georgia among Army active duty trainees. Use of a hygiene strategy that included chlorhexidine along with an educational component averted more costs and days lost in training compared to the other two strategies. Upon further inspection, these findings were impacted when evaluated by training site, phase,

and season of training. Additionally, the type of infection (SSTI overall vs MRSA SSTI) had a differential effect on the cost effectiveness of the strategy.

Until now, uncertainties surrounded the true time and cost burden of overall, *S.aureus,* and MRSA SSTI within the Army active duty recruit training population. Results from this study showed a considerable amount of lost time in training and cost burden, especially during certain training times (the beginning of training). Additionally, although results have varied with respect to the effects of hygiene strategies on acute, communicable infections risks, analyses revealed that there could be potential benefit in using these strategies in the community setting. A prospective study did contradict these findings, showing no effect on rates of SSTI overall or MRSA SSTI. A cost effectiveness analysis was performed that took into consideration the results from the prospective trial and used outcomes such as costs and time averted. In doing so, initial results showed that a strategy that includes a chlorhexidine component along with hygiene education can be cost effective. All this information combined is a good first step in the research process to identify suitable primary prevention measures to implement within a recruit training environment. Further measures should be taken to determine if these strategies are indeed appropriate for this population. Research should not stop here; rather it should extend into trainee populations other than the Army and outside the military setting altogether into other community settings at high risk for overall, *S.aureus* and MRSA SSTI. In conclusion, although a clear intervention strategy was not identified to prevent these infections within the recruit population, the methodology used to identify *S.aureus* and MRSA SSTI cases as well as LTT and COI, should be incorporated into future military

medical health surveillance data sources to more accurately estimate burden of disease in this population.

ACRONYMS

CEA	Cost effectiveness analysis
CER	Cost effectiveness ratio
ICER	Incremental cost effectiveness ratio
BOI	Burden of illness (IDCRP-066)
FBS	Fort Benning study (IDCRP-055)
SP	Standard practice
SP BOI	Standard practice estimates from BOI IDCRP-066
SP BOI FB	Standard practice estimates from BOI IDCRP-066 Fort Benning OSUT site only
OSUT	One stop unit training
CHG	Chlorhexidine group
ES	Enhanced Standard
HHP	Hand hygiene promotion
PHP	Personal hygiene promotion
MCSA	Monte Carlo sensitivity analysis
C	Costs
E	Effects
LTT	Lost time in training (days)
USD	United States Dollars
SSTI	Skin and soft tissue infection
SA	*Staphylococcus aureus*
MRSA	Methicillin resistant *Staphylococcus aureus*
CA	Cost averted
LTTA	Lost time in training averted
I&D	Incision and drainage
Cx	Culture
P	Purulent
NP	Non purulent

DEFINITIONS

Trainee	Army active component service members with a rank of E1 to E4 who served at one of the five Army One Stop Unit Training (OSUT) locations during an Army-specific training period following a first ever service record.
Recycled	Any soldier who is delayed in the completion of training due to repeating certain phases of training. This includes personnel delayed for medical reason.
Skin and soft tissue infection	ICD-9-CM codes 680-686.8 which are categorized under "Infections of the Skin and Subcutaneous Tissue". These codes include: 680-680.9 "carbuncle and furuncle"; 681-681.9 "cellulitis and abscess of finger and toe"; and 682-682.9 "other cellulitis and abscess".
Purulent infection	Cellulitis and abscess" diagnosis with a culture, "abscess" clinical manifestation or an "incision and drainage" procedure with MRSA coverage or folliculitis, carbuncle/furuncle, or pilonidal cyst with abscess diagnosis.
Non purulent infection	Infections lacking abscess-like manifestations, procedures indicative of abscess, and no MRSA coverage
Staphylococcus aureus	Clinical culture positive for *S.aureus*
Methicillin resistant *Staphylococcus aureus*	(1) *S. aureus* culture confirmed positive (2) confirmed resistance towards oxacillin or otherwise confirmed as MRSA by clinical microbiology.

Hand hygiene promotion	• Hand washing
	  o Soap and water
	  o Antibacterial soap and water
	• Hand sanitizing
	  o Non-alcohol based hand sanitizer
	  Alcohol based hand sanitizer
	• Hygiene education

Personal hygiene promotion	• Showering/bathing
	  o Chlorhexidine
	  o Hibiclens
	• Hygiene education

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CHAPTER 1 Introduction

STATEMENT OF THE PROBLEM

For more than a decade now, multiple reports have been published on outbreaks of methicillin-resistant *Staphylococcus aureus* (MRSA)-associated skin and soft tissue infections (SSTIs) in community settings. Studies have cited increased emergency room visits for SSTIs and attribute most of these visits to the emergence of community-acquired MRSA (CA-MRSA). Since 1960, MRSA has been associated with hospital settings; only over the past two decades have MRSA infections increasingly presented in the community environment. Numerous CA-MRSA outbreaks have occurred in congregate populations like military trainees, but limited or non-existent information is available regarding CA-MRSA's impact (in terms of disease rates and cost) on U.S. Military Forces, specifically in the training environment. In an era of emerging antimicrobial resistance, increased emphasis recommendations have been made to direct efforts toward prevention. Lack of clear and consistent evidenced-based community SSTI prevention methods have been cited in the literature. The primary elements of community-based SSTI prevention recommendations are improved personal hygiene, education, and environmental disinfection. Information regarding the effect of such strategies on the incidence of SSTI and MRSA-associated SSTI has not been fully explored in a systematic fashion. A comprehensive systematic review of the literature is necessary to assess the best available practices to prevent MRSA-associated SSTI. Last, more needs to be done to translate the results of systematic studies into a cost-effectiveness analysis to more fully understand the impact of prevention efforts on SSTI and MRSA-associated SSTI, to inform DOD policy.

BACKGROUND

Staphylococcus aureus (*S. aureus*) infections are widespread in the USA, and commonly manifest as skin and soft tissue infections (SSTIs) such as boils, abscesses, furuncles, folliculitis and cellulitis ranging from minor wounds to life-threatening conditions. One systematic review suggest that of the patients with cellulitis that had positive cultures up to 50% had cultures positive for *S. aureus* and 27% for group A s*treptococcus*. (44) Complications of infection include endocarditis, bloodstream infections, surgical wound infections, urinary tract infections, osteomyelitis, and pneumonia. (4; 67; 71; 73; 82; 144; 193) An increasing proportion of *S. aureus* infections have become resistant to beta-lactams. A number of infections can be attributed to methicillin-resistant *S. aureus* (MRSA). (73; 144) In the past, methicillin-resistant *S. aureus* (MRSA) was primarily considered a hospital-associated (HA) organism, but outbreaks have been reported in closed populations, such as in prisons and military training environments. Infections can be spread through sharing of equipment, towels, benches, and personal items. (42; 66) Community-associated MRSA (CA-MRSA) has been increasing globally over the past two decades. (51; 84; 93; 212) A number of studies have tried to distinguish CA MRSA from HA-MRSA. (67; 69; 139; 141) CA-MRSA infections are believed to differ from HA-MRSA infections with regards to distinct epidemiology, pathogenesis, bacteriological characteristics, and clinical manifestations.(69; 93; 141; 153) Although distinctions between the two have been made, the differences have been blurred in recent years. The Centers for Disease Control's (CDC) criteria for CA-MRSA include persons with MRSA infection who meet the following criteria: (1) Diagnosis of MRSA made in the outpatient setting or by a culture

positive for MRSA within 48 h after admission to the hospital, (2) no medical history of MRSA infection or colonization; (3) no medical history in the past year of hospitalization, admission to a nursing home, skilled nursing facility, etc.,.(139; 141)

Host risk factors include crowding, poor hygiene, compromised skin integrity, and frequency of skin to skin contact. (170; 190; 212) Additionally, Some studies have suggested that fomites can be sources of microbial transmission.(140) Many infections occur in close contact settings such as those individuals who are housed in close quarters for extended periods of time. (160; 190; 212)

CA-MRSA colonization is believed to be a mode of transmission in community settings, but a conceptual model suggests that CA-MRSA acquisition may arise from a variety of factors that may ultimately result in infection. The model "the 5 C's of CA-MRSA transmission developed by the Centers for Disease Control and Prevention (CDC) indicates MRSA infection could result in direct skin-skin Contact, cleanliness, Compromised skin integrity, Contaminated objects or surfaces, and Crowed living conditions.(140) Exposure to antibiotic agents may also play a role in MRSA infection or colonization. (127; 140; 172) This model has not been fully explained outside the outbreak setting.

SSTI and MRSA-associated SSTI Epidemiology in the United States

Most studies that have tried to estimate the number and rate of SSTI and CA-MRSA-associated SSTI in the United States have been conducted in ambulatory care or outpatient settings. The true prevalence of disease is unknown due to the lack of large population based studies. Most studies conducted have used national datasets and urban sentinel surveillance sites. Estimation of community-acquired SSTI and MRSA-

associated SSTI is difficult and most studies have occurred in specific community populations (like ER's) or the outbreak setting. Since most studies have been conducted in various settings, predictors of disease are also mixed. One factor remains constant; the proportion of *S. aureus* infections attributable to CA-MRSA has increased substantially since the 1990s. (51)

Multiple descriptive, observational studies have attempted to elucidate the burden attributable to SSTI in the community as opposed to the hospital setting. (73; 74; 132) A descriptive study using data from the National Ambulatory Medical Care Surveys and National Hospital Ambulatory Medical Care Surveys from 1992 through1994 and 2001 through 2003 aimed to estimate the number and rate of ambulatory care visits in the United States for SSTI likely caused by *Staphylococcus aureus* (*S. aureus*). Results showed a total of 11.6 million annual visits were made to US ambulatory care providers for selected SSTI which represented about 1% of all visits. From 2001- 2003 the overall visit rate was 410.7 per 10,000 persons compared to 376.3 per 10,000 person from 1992-1994. Visits increased in all SSTI categories (carbuncle/furuncle; cellulitis and abscess of finger and toe; other cellulitis and abscess; and other specified diseases of hair and hair follicles) except for "impetigo" and "other SSTIs". The largest increase between the study periods was observed for "other cellulitis and abscess" with a 26% increase in visit rates.(132)

Multiple outbreaks of CA-MRSA SSTI have occurred nationwide, most notably among athletes, prisoners, and military training populations. (55; 106; 155; 163; 216) Reports of outbreaks have also been reported among religious communities, health care workers in the outpatient clinic setting, and even among children in daycare facilities.(50;

104; 180) The most common clinical manifestations in all these outbreaks were cellulitis, abscess, folliculitis, paronychia, and furuncles. Outbreak investigations in community settings revealed that sharing of soap and towels, skin injury, and close contact were potential risk factors for skin infection, but multivariate analysis results showed sharing of soap and towels to be a significant predictor for CA-MRSA infection (OR: 12.1, 95% CI 1.83-68.0, p=0.006)(155). Additionally, one multivariate analysis found antimicrobial use within 12 months before infection (OR: 11.7, 95% CI 2.9-47.6, p=0.006) was associated with infection. (50)

Burden in the military

Military trainees are known to be at high-risk for SSTIs such as cellulitis and abscess, and a significant proportion of these infections are caused by CA-MRSA.(40; 216) Outbreaks of MRSA-associated SSTI have been well described in military settings but less I known about the burden of these infections on the military healthcare system.(8; 9; 28; 51) Disproportionately higher rates of overall and MRSA-associated SSTIs among military training populations can result in an increased health care burden and impairment in the ability of soldiers to participate in and successfully complete training programs. Additionally, beyond the training setting, CA-MRSA-associated SSTIs are encountered with greater frequency in deployed soldiers.(165)

The Armed Forces Health Surveillance Center (AFHSC, formerly Army Medical Surveillance Activity (AMSA)) published two descriptive surveillance reports regarding cellulitis and abscess in the active duty military population in 2002 and 2006. (8; 9) In the studies, surveillance data were reviewed to identify all incidences of ambulatory visits and hospitalizations among active duty service members with either a primary diagnosis

of cellulitis or cellulitis/abscess-specific diagnosis. The data used were derived from the Defense Medical Surveillance System (DMSS). The 2002 study showed results from 1998-2001 and the 2006 study showed results from 2002-2005. Over the two study periods the overall incidence for cellulitis and abscess increased by 40%, with a rate of 19.1 cases per 1,000 person-years in the 2002 study and a rate of 32.4 cases per 1,000 person-years. The 2006 study found that most cases and highest rates were at installations that conduct recruit training. The 2002 study found that most cases occurred amongst those with less than six months of service. In each service, the most cases that occurred the first six months of service occurred during the weeks that corresponded to basic or recruit training-with those weeks being during times of heavy physical activity.(8)

The AFHSC also issues annual surveillance reports regarding ambulatory visits, hospitalizations, and health care burdens attributable to various diseases among active duty service members. These reports include information on incidence, rates, and trends over broad disease categories as well as more specific diagnoses, such as "other cellulitis and abscess".(40) The number of ambulatory visits and hospitalizations for "skin and subcutaneous tissue" over the past ten years continuously remain in the top ten diagnostic categories among all active duty service members. The overall number of diagnoses of "other cellulitis and abscess" during ambulatory visits and hospitalizations increased the most between 2000 and 2004 and then remained relatively stable from 2005 forward (**Figure 1**). The report showed in 2009 for skin disease (not contact dermatitis or sebaceous gland disease) there were over 270,000 medical encounters, almost 150,000 individuals affected, and 9800 hospital bed days.(40) In the same report, a brief surveillance snapshot of illness and injury burdens among U.S. military recruits (defined

as active component members of the Army, Navy, Air Force, or Marine Corps with enlisted ranks of E1 (Private) to E3 (Private First Class) who served at one of the nine training locations) showed skin infections ranked 4th behind respiratory infections, injury, and signs/symptoms disease burden categories in terms of medical encounters (≈30, 000) and individuals affected (≈15, 000).(40)

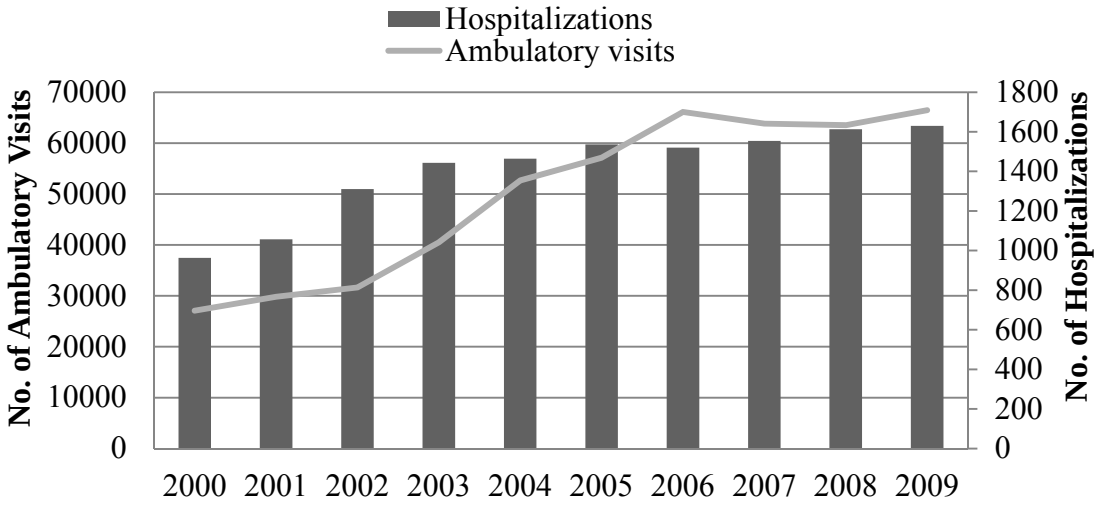


Figure 1 Ambulatory visits and hospitalizations for cellulitis among Active Duty Military Component from 2000 through 2009.Derived from MSMR surveillance reports.(10; 40)

In the Army specifically, those recruits waived for unspecified skin problems all had higher levels of attrition over time than their matched comparison counterparts.(157) Niebuhr et al reported that unspecified skin conditions accounted for 4% of hospital admissions within the first year of service from 1996 to 2001, this is important considering hospitalization is usually a precursor for attrition within the first year of service.(157)

The Navy Marine Corps Public Health Center (NMCPHC, formerly known as Navy Environmental Health Center (NEHC)) attempted to identify outpatient diagnosed SSTI associated with MRSA from 2006-2008 among all active duty military service

members located in the United States.(46) To conduct their study they used data from the Department of Defense's Standard Ambulatory Data Record (SADR) and Health Level 7 (HL7) microbiology and outpatient pharmacy datasets. They found approximately 360,000 cases of SSTI among active duty military service members, of which 49% were incident cases. Of the cases, most were male and between the ages of 20 and 29. After matching clinical specimens with the case and removing duplicates, only 10% of SSTI cases remained. They found that 74% of the identified isolates associated with SSTI were positive for *S. aureus*. Two-thirds of the *S. aureus* isolates were identified as MRSA. Most of the MRSA cases were female (72%) and younger than 20 years of age (72%). Resistance towards both oxacillin and erythromycin was observed among SSTI associated isolates.(46)

Finally, a study was done using surveillance data from the Martin Army Community Hospital at Fort Benning, Georgia, from 2002 through 2007. (144) The data captured information on culture-confirmed MRSA cases. Of the 6,560 *S. aureus* isolates, 65% were identified as MRSA, of which 82% met the case definition for CA-MRSA. A total of 3,175 unique infections were observed, with some cases experiencing up to 5 infections. Monthly rates of CA-MRSA reached 7.2 cases per 1,000 soldiers in October 2005 and annual rates peaked around 41.4 cases per 1,000 soldiers in 2005. Most of the cases were among individuals less than 24 years of age (76%), males (97%), and were assigned to the Infantry Training Brigade (ITB) (58%). During the six year period, there was an average of 3 patient visits (±2 visits, range 1-30 visits) that were associated with infection, amounting to 10,854 patient visits. Collected disposition data from 2005-2007 revealed that 39% of infections resulted in a limited duty profile which lasted an average

of 5.3 days resulting in a total of 5,046 limited duty days during the study period. About 10% of the cases required hospitalizations. Approximately half of the cases were prescribed antibiotics and 82% of cases who were prescribed antibiotics received an antibiotic classified as effective. (144)

Although the current data are helpful, they have limitations. Estimates of SSTI disease burden in the active duty (AD) military trainee population based on comprehensive, clear, and rigorous methods are needed. A complete evaluation on the burden of SSTIs in the active duty military trainee population has not been done. Most of the surveillance reports cited above included many components to assess burden such as numbers, rates, and trends of cellulitis and abscess among the active duty component service members, but were limited by the type of data that were used or available. Many of the surveillance reports give a broad general sense of the burden of SSTI in the active duty military population, but not the trainee population. Most of the assessments in the surveillance reports were done by using data obtained through the DMSS.(167) While robust, this system does not include laboratory, pharmaceutical, or cost information which cannot allow for more in depth analysis of disease burden. Without SSTI wound culture information, antibiotic prescription and clinical procedure information, it is difficult to assess the burden attributable to *S. aureus* (MRSA specifically). The study done using SADR and HL7 data only analyzed the number and proportion of SSTI and MRSA-associated SSTI among active duty service members and did not evaluate any active duty military trainee-specific subgroups. The descriptive analysis did have trainee specific information available, but the data were limited to the installation in which they were collected and did not include specifics on SSTIs.

Multiple uncertainties still exist regarding the burden of SSTI and CA-MRSA-associated SSTI in the active duty military trainee population, the burden in certain trainee subpopulations (e.g. branch of service, rank, assigned duty station), health care utilization among trainees diagnosed with an SSTI (e.g. visits to the physician, antibiotics prescribed, procedures done, etc.), and finally the direct and indirect costs associated with SSTI and MRSA-associated SSTI. Previous studies have tried to elucidate these uncertainties, but questions remain. Using a combination of data sources that include patient, pharmacy, microbiologic, and cost information could assist in answering questions regarding the burden and costs of SSTI and MRSA-associated SSTI in the active duty military trainee population.

Cost of SSTI and MRSA-Associated SSTI

Economic impact analyses such as the cost of illness (COI) falls within measuring the burden of disease. Mortality, morbidity, and life expectancy, all measure disease burden related to a health outcome. Cost of illness analysis represents another measure of disease burden that incorporates cost of disease.(115) Costs associated with SSTI can be measured as direct medical costs (e.g. outpatient care, hospital care, laboratory procedures, prescription, etc.) and indirect costs (e.g. morbidity). Few studies have attempted to address costs of SSTIs or MRSA-associated SSTIs in the United States. Most importantly, no peer-reviewed evaluations exist regarding costs of SSTI or MRSA-associated SSTI in active duty military trainee populations. Five studies were identified in a literature search regarding this topic. 51-55(**Appendix A**) Of the studies that have explored the SSTI cost burden in the United States, most have focused on the inpatient population or complicated skin and skin structure infections (cSSSIs). Two studies

attempted to explore costs in outpatient settings, of which only one determined cost of SSTI due to *S. aureus*.(58; 129) Additionally, of the cost studies identified regarding MRSA all have been performed in the inpatient setting.(111; 136) Cost estimates varied with each study. Total costs calculated for MRSA-associated infections were as low as $4500 per case up to $35,000 (**Appendix A**). The wide range exemplifies the differences in the components of the cost calculations as well as the variations in how illness was evaluated.

Obviously, with the sparse number of (COI) studies related to SSTI in the community setting, many uncertainties still remain, especially with regards to cost of SSTI and MRSA-associated SSTI in the active duty military population overall and more specifically the active duty military trainee population. Two studies cited above did attempt to evaluate costs of SSTIs in the outpatient setting and one even tried to determine the cost of SSSIs due to *S. aureus*. (58; 129) The studies were limited by the type of data available. Inherent problems exist in using medical databases as studies try to draw conclusions about the outpatient population vs. the inpatient population. Many assumptions were made concerning the criteria for an outpatient or an inpatient. In Marton's study, SSSI costs were calculated using medical claims data. When researchers attempted to calculate costs associated with *S. aureus*-related SSSI, they used ICD-9-CM codes that were often incomplete like organism resistant to penicillin (V09.0) or diagnosis of MRSA. Medical charts and microbiologic data were unavailable to confirm SSSI and associated *S. aureus* diagnoses. The Dehkharghani study, although it used a well-recognized framework, was limited by the numerous databases used to estimate costs associated with SSTI. The study also lacked a clear assessment of the population

affected by the costs. Costs were lumped into broad categories of ICD-9-CM codes for skin disease and then examined by ambulatory costs, inpatient costs, and drug costs. Using such methods, costs could have been overestimated. Both studies also used varying methods to estimate costs associated with SSTI. Also information regarding costs of lost productivity was not available.

A study of the cost of SSTI and MRSA-associated SSTI among active duty military trainees is important for a number of reasons. A COI study is necessary to provide a comprehensive estimate of SSTIs and MRSA-associated SSTI on the military health care system. Second, trainees are an at risk population for acquiring an SSTI and MRSA-associated SSTI. Understanding the costs associated with care and treatment of an active duty military trainee can better direct allocation of resources (e.g. where patient should receive care or how patients should receive care). Even further, understanding the costs associated with lost productivity in addition to direct medical costs is important, as each lost recruit costs DoD approximately $35,000 to recruit, access, and train a replacement.(158) In the advent of new prevention measures to reduce SSTI and MRSA-associated SSTI in the trainee population, cost estimates generated from this study can serve as a baseline for comparison (i.e. treatment vs. prevention) for cost effectiveness analysis. A detailed assessment of the costs of SSTI and MRSA-associated SSTI can influence both patient care and prevention policy.

Personal Hygiene-Based Prevention

Recommendations

The Centers for Disease Control (CDC), Federal Bureau of Prisons (FBOP),National Collegiate Athletic Association (NCAA), and military services such as the U.S. Army, Navy, and Marine Corps have developed guidelines geared toward prevention of Staphylococcal infections, like MRSA, that cause a majority of SSTIs in the community, prison, sports, and military settings, respectively.(2; 109; 151; 154; 195; 196) Recommended prevention strategies include several similar components regarding hand hygiene, personal hygiene practices, education pertaining to infection identification and modes of transmission, surveillance of local lab cultures, and standard environmental cleaning practices with EPA approved agents. Additionally, these organizations provided guidance on standardized care consistent with the prevalence of infection and susceptibility patterns in the geographic area. Most of the guidance developed was in response to numerous MRSA-SSTI outbreaks that have occurred in close contact community settings. Comparisons of recommendations are provided in **Appendix B**.

Literature review

Multiple studies assessed the various components' of the above recommendations effectiveness on reducing infections caused by different microbial agents like MRSA. A table of the literature, provided in **Appendix C**, shows the number of studies found that pertain to hygiene practice, study design and population in addition to outcomes measured. Of the studies found, most hand/personal hygiene or hygiene education studies assessed gastrointestinal illness (GI) and respiratory illness (RI) outcomes while studies

of chlorhexidine and sanitation focused mostly on SSTI, MRSA, and Vancomycin Resistant *Enterococcus*.

Education

Education seems to be an important element in prevention of infection. A meta-analysis by Aiello et al showed that use of education alone prevented 31% of GI cases compared with no intervention and education combined with use of non-antibacterial soap prevented 51% of RI compared with no intervention in a control group. An RCT of a multifaceted intervention to include alcohol-based hand sanitizer and hand-hygiene education to reduce GI and RI in the home found secondary GI illness rate was significantly lower in the intervention group compared to the control group. Rates of RI did not differ significantly between the groups.(173) Unfortunately, it is difficult to tease out which element of the multifaceted intervention contributed the most to reduction in secondary GI illness rates as the program was evaluated as a whole.

Little is available with regards to how effective education techniques and early recognition are on CA-MRSA prevention. In a 2009 study of such measures as providing education booklets, posters and videos to college athletes, results showed a 75% reduction in infections.(172) This study was not a randomized controlled trial; it was based more on a theoretical framework and only evaluated absolute number of cases. Without a systematic approach to the evaluation, it is difficult to determine which component of the educational program actually contributed to the overall reduction in cases.

Hygiene-based prevention

Hand washing interventions could decrease risk of acquiring infections (202). One study found that poor hygiene practices resulted in increased risk for MRSA infections in a prison population.(194) Studies on prevention and control of infections that include personal hygiene measures (i.e., hand sanitizer application or hand washing) have been shown to be effective at reducing respiratory and gastrointestinal infections among populations like military recruits.(148; 169) One prospective cohort study evaluated the use of hand sanitizer and education among Army recruits. Results showed significant decreases in GI and RI. When compared to a control group, the intervention group experienced 48%, 40%, and 44% less GI, RI, and lost time in training, respectively. Another study among Navy recruits examined the use of non-antibacterial soap and water; it showed a 45% reduction in total outpatient visits for RI.(169) Less is known about personal hygiene measures' effect on incidence of SSTI (like cellulitis or abscess)in the community setting but such measures seem effective in stemming MRSA outbreaks among military (38; 216) and similar congregate populations like athletes and inmates.(106; 215) Personal hygiene is believed to play a major role in SSTI and MRSA-SSTI and is considered an important measure for limiting its spread.(215)

Chlorhexidine gluconate wash

Chlorhexidine gluconate (CHG) has been used as an antimicrobial agent for a number of years. Its bactericidal activity is dependent on its concentration; most chlorhexidine hand wash products come in 2-4% concentrations. Usually at this concentration, it exhibits bactericidal activity against *S. aureu*s.(105; 133; 143) Chlorhexidine is often used to disinfect skin of its natural flora. One study found that

chlorhexidine reduced bacterial counts from 86% to 92%, depending on its concentration. Chlorhexidine not only has a greater effect on immediate reduction of skin flora but also has continued residual antibacterial activity against *S. aureus*.(122; 185)

Chlorhexidine used as a hand wash or body wash has been evaluated primarily in the clinical setting by observing its effects on eradication of MRSA.(183; 205; 208) Reviews are mixed regarding its effectiveness in reducing bacterial colonization and preventing infections. In theory, MRSA carriage eradication should reduce risk of MRSA infection and prevent transmission to other patients.(183) Results from an evaluation of the effects of a 7-day combined course of chlorhexidine gluconate washes, intranasal 2% mupirocin, and oral rifampin and doxycycline showed successful MRSA decolonization among hospitalized patients. The study did not evaluate the individual components' effects on MRSA decolonization; therefore, it is unclear as to which component actually provided the most benefit with regards to MRSA decolonization.(183) Another study of whole body washing with Chlorhexidine, found that overall it was not more effective in overall eradication of the MRSA but was effective in reducing bacterial colonization of the skin.(208) Johnson et al introduced a hand hygiene program involving the use of an alcohol/chlorhexidine solution along with alcohol-impregnated wipes, mupirocin and triclosan body washes, and a culture-change program to reduce rates of hospital MRSA infections. By the end of the program, the rate had decreased by 40% compared with the baseline.(103) Last, a cluster-randomized trial attempted to chlorhexidine impregnated cloths during a 6-week training cycle to prevent SSTI among Marine recruits, but no differences in rates of SSTI were observed between comparison groups.(213)

Environmental disinfection

The environment has been documented as being a source of MRSA or being involved in its transmission (89), but it is not clear how important this is relative to other factors (e.g. personal hygiene, education). Fomites are thought to play a role in outbreaks of CA-MRSA.(140) Emphasis on environmental decolonization could be a key component in preventing infection. High touch surfaces such as wrestling mats or exercise equipment can potentially be a vehicle to transmit MRSA from contact with hands.(100; 140; 178; 186)

Most research on environmental disinfection has occurred in the hospital setting. (92; 98; 131) Improvements in cleaning have shown significant reductions in infections like, vancomycin-resistant *Enterococcus* (VRE). Prevalence of VRE declined by 6% with every 10% increase in percentage of sites cleaned (98) and surface contamination decreased in one hospital after enforcing routine environmental cleaning measures.(92) *Clostridium difficile*-associated diarrhea incidence decreased from 8.6 to 3.3 cases per 1000 inpatient days post-intervention after using a hypochlorite solution.(131) One systematic review attempted to explore the extent environmental clean contributed to control of MRSA infection and concluded that effectiveness of environmental cleaning is important to preventing transmission of MRSA.(121)

Systematic review of hygiene-based prevention strategies

A need exists to evaluate the effectiveness of the above recommended hygiene practices for prevention of infections like SSTI using systematic methodology. The review should evaluate a strategy's effectiveness on prevention of not only on HAI, GI,

and RI, but also SSTIs like cellulitis and abscess. A systematic review of this nature is lacking in the literature.

Reviews have been published regarding CA-MRSA associated SSTIs and have attempted to define CA-MRSA, describe its emergence as a public health threat, provide insight into the pathogenesis of the infection, as well as describe the clinical spectrum, microbiology, and epidemiology of CA-MRSA.(44; 79-81; 139; 141; 190; 204) Additionally, reviews have summarized CA-MRSA clinical management, transmission prevention, and primary prevention measures in communities such as athletes and correctional facility inmates.(25; 47) Reviews and meta-analyses have also been done to explore the attributable-risk and potential risk factors for MRSA among military recruits and prison populations.(7; 59; 170; 194)

A brief literature search resulted in five systematic reviews that evaluated the effectiveness of hygiene practices such as showering with skin antiseptics (205); use of hand sanitizer, antibacterial, or non-antibacterial soap with or without education (5; 53; 205); hand washing (53); and disinfection of environmental surfaces (59; 121), on surgical site infections (SSIs), gastrointestinal (GI) and respiratory illness (RI), and hospital-acquired illness (HAI), respectively. None of the analyses examined the effectiveness of such practices on SSTI. Furthermore, varying methodologies were used in each of the reviews. A systematic review with consistent methodology is warranted.

Cost-effectiveness analysis

Prevention is deemed to be the best measure in reducing the incidence of MRSA infections, but often considered too costly with uncertain effectiveness outcomes.(41; 182) Cost-effectiveness studies available regarding prevention and control of MRSA

infections pertain mainly to the hospital environment. (119; 150) Infection control measures in the hospital settings include early identification of MRSA through active surveillance of cultures, contact isolation, and standard precautions.(41; 209) (36; 119; 150; 182) Such measures have been shown to improve patient outcomes and reduce prevalence and incidence of colonization and infection as well as healthcare costs.(151)

Two cost-effectiveness analyses were conducted to evaluate universal MRSA screening measures. Lee et al developed a stochastic computer simulation model to determine the economic impact of performing MRSA surveillance for all hospital admissions at different MRSA prevalence and basic reproductive rates. Results indicated that when the basic reproductive rate was 0.25 or greater and the prevalence was 1% or greater, universal MRSA surveillance was cost-effective (defined as an incremental cost-effectiveness ratio (ICER) < $50,000 per quality-adjusted life-year).(119)

Murthy et al. assessed the cost-effectiveness of three hospital-based screening strategies: (1) PCR screening; (2) screening for risk factors combined with pre-emptive isolation and contact precautions pending chromogenic agar results; and (3) no screening, using a decision analytic model from the hospital perspective. Costs were expressed in 2006 Swiss Francs (CHF). Strategies 1 and 2 were found to be more costly (10 502 CHF and 10 511 CHF, respectively) than standard surgical admission without screening (10358 CHF), but both had a lower infection probability compared to strategy 3 (0.0041 and 0.0057 vs. 0.0088, respectively). Sensitivity analysis showed that prevalence of MRSA carriage influences the incremental cost-effectiveness ratio (ICER); higher prevalence improves the cost-effectiveness and moves PCR screening toward cost-neutrality compared to admission without screening.(150)

The studies noted above do not evaluate cost-effectiveness of community-based MRSA prevention strategies, but they do provide estimates and methodologies that could be used in future analyses. Simulation techniques, comparison of multiple programs using a decision-analytic framework, and incremental cost-effectiveness ratios will all be used to assess the cost-effectiveness of prevention strategies.

Although improved hygiene is recommended to reduce MRSA-associated SSTI infections, cost-effectiveness studies are scant with regards to this topic in the community. Only one study, in the hospital setting, attempted to evaluate the cost-effectiveness of hand hygiene compliance. According to the authors, improved hand hygiene compliance among healthcare workers could be cost saving (52). Cummings et al. developed a stochastic mathematical model to simulate the outcome of a single episode of hand hygiene noncompliance. Authors concluded that noncompliance was associated with significant attributable hospital cost with the mean cost per noncompliant event being $52.53 (95%CI, $47.73-$57.32). Results showed that a 1.0% increase in hand hygiene compliance could result in annual cost savings of about $40,000 to a 200-bed hospital.(52)

Another study in the college student athlete population evaluated an organized CA-MRSA prevention education program on cases of MRSA-associated SSTI. Authors theorized that such a program would not require invasive or pharmacological measures; and would stand a greater chance of acceptability, sustainability, and indoctrination into other college football programs. The program consisted of three components (a) an educational session for players and coaches/trainers (b) educational booklets and posters, and (c) strategically placed MRSA deterring hand-sanitizing wipes. Over the course of

the study it was shown that this program had reduced the number of CA-MRSA or SSTI by 9.6 cases (>75%) (172). Authors of the same study also tried to assess cost-effectiveness of the program. Although the program achieved the desired effect, questions remained about the sustainability of the program. Average savings were divided by the costs of the program. The program had a return of $4.51 to $11.29 in health care savings.(172)

Most of the studies described above used decision analytic models but did not use individual level data; instead, authors retrieved data points from the literature. Of the cost-effectiveness studies described above, only one used prospective cohort data, the other two studies simulated the cost-effectiveness models using estimates from the literature. The proposed cost-effectiveness study aims to use not only estimates from the literature to simulate a hypothetical cost-effectiveness model of hygiene practices influence on SSTI; but data will also be obtained through a 20-month cluster-randomized controlled trial which is described in more detail in the following preliminary studies section.

As previously stated, scant cost-effectiveness literature exists on hygiene practices to prevent SSTI or MRSA-associated infection in the community population. No previous literature exists regarding cost-effectiveness of strategies to prevent SSTI and MRSA-associated SSTI in the active duty military population, specifically the trainee population. Evaluations of the cost-effectiveness of MRSA prevention strategies have generally been limited to the clinical setting. Uncertainties remain regarding costs and effects associated with a community-wide program that includes simultaneous implementation of multiple

hygiene-based measures on infection rates. Cost-effectiveness of such a program has yet to be determined in a prospective fashion; therefore, further assessment is warranted.

Progress/Preliminary Studies

A multi-component hygiene-based intervention at the Marine Corps Recruit Depot –Parris Island (MCRDPI) was associated with a significant decrease in MRSA SSTIs. The prevention strategy at MCRDPI included: [1] standardized personal hygiene practices, [2] periodic chlorhexidine showers upon entry into training and during times of rigorous field activity, and [3] recruit and drill instructor MRSA education regarding identification and reporting of infections.(144; 146)

We reviewed MCRDPI disease surveillance data from 2003-2008 to assess the impact of this strategy on rates of SSTI and MRSA-associated SSTI. The annual numbers of cases of SSTI and MRSA-associated SSTI during this time period ranged from 1479-2495 and 211-1051, respectively. Annual SSTI rates peaked at 544 per 1000 person-years in 2004 and, following the December 2005 implementation of the intervention, declined thereafter to 298 per 1000 person-years in 2008. SSTI rates in the post-implementation period (2006-2008) were 29% lower than the pre-implementation period (2003-2005). Similar trends were observed for MRSA-associated SSTI, namely a decrease in annual rates from 229 per 1000 person-years in 2004 to 45 per 1000 person-years in 2008, and a 65% rate reduction from the pre-implementation time period. During periods of high incidence (May through October), the rates of SSTI and MRSA-associated SSTI again declined following the implementation of the intervention in 2005.(144-146)

An 20 month prospective evaluation of similar personal hygiene-based prevention strategies listed above was conducted among military trainees at Fort Benning, Georgia

(138). In general, weekly chlorhexidine wash was compared with a basic approach (preventive medicine briefing) and an enhanced standard (extra education among trainees and drill instructors and once weekly 10 min shower with soap and water).(65)Trainees were offered various intervention components depending on the battalion to which trainees were assigned. The investigation began in May 2010 and ended on Dec 2011. The study population was comprised of Army Infantry One Station Unit Training (OSUT) trainees entering training from May 2010 through December 2011. This population was all male, between the ages of 17 and 40 years old, ethnically diverse, and in generally good physical condition.(65)

RESEARCH PROPOSAL

Overall research question

What personal hygiene-based prevention strategies have the greatest impact on rates of SSTI and MRSA-associated SSTI in the active duty military trainee population and which strategies are most cost-effective?

Objectives and Specific Aims

This study will evaluate the current burden of SSTI and MRSA-associated SSTI in the Army active duty military trainee population, effects of personal-hygiene based SSTI prevention programs, and the cost-effectiveness of SSTIs prevention programs. The **long-term goal** is to implement the most cost-effective hygiene-based strategy to prevent SSTIs and MRSA-associated SSTIs in the active duty military trainee population. The **overall objective** is to estimate the incremental cost-effectiveness ratio to identify the best measures that incur minimal costs along with being effective. The **central hypothesis** is that personal hygiene-based prevention strategies can reduce rates of SSTI

and MRSA-associated SSTI and can be cost-effective. The **rationale for the study** is that persons in community setting are increasingly becoming infected with antimicrobial resistant organisms and this trend has been reflected among active duty service-members, especially trainees. This evaluation will provide more insight regarding the costs associated with implementing a hygiene-based prevention program aimed at reducing SSTIs caused by organisms such as *Staphylococcus aureus* (*S. aureus*). Such knowledge will allow for more informed decision making with regards to implementing programs aimed at reducing such infections in congregate settings, like the military training environment. Previously published reports recommend the use of hygiene-based prevention programs to reduce skin and soft tissue infections in outbreak settings, but little has been done to evaluate how effective these measures are at preventing SSTI and MRSA-associated SSTI compared to the current standard of care. In the advent of antibiotic resistance, it is important to implement cost-effective SSTI prevention measures, reducing the requirement for antimicrobial therapy. This research could yield substantial benefit not only in the military setting but could possibly be translated to other similar congregate populations. Identifying costs associated with instituting a hygiene-based prevention program will allow policymakers to make a more informed decision.

Objective 1: Examine military health system datasets to assess the distribution, trends, and predictors of SSTI and MRSA-associated SSTI clinic, hospital, and lost-time burden among the active duty Army training population from 2006 to 2009.

Specific aim 1: Estimate the frequency, incidence-density rates, trends and distributions of trainees affected by SSTI and MRSA-associated SSTI by performing retrospective, descriptive analyses of military health databases.

Specific aim 2: Calculate the frequency and incidence-density rate of outpatient medical encounters and hospital admissions; and the number and percent of prescribed antibiotics, procedures performed, and laboratory tests ordered due to SSTI and MRSA-associated among trainees to assess clinic and hospital burden. Measure the seasonal impact on healthcare utilization.

Specific aim 3: Calculate the total number of training days lost among trainees due to SSTI and MRSA-associated SSTI.

Specific aim 4: Measure associations and assess possible risk factors for SSTI and MRSA-associated SSTI rates through univariate and multivariate statistical measures.

Significance: Estimates generated from this analysis serve two purposes. They will provide baseline information regarding the burden of SSTI and MRSA-associated SSTI in the active duty military trainee population. Information gathered also will be used for comparisons in analysis of subsequent objectives. Additionally, information obtained from this descriptive study can potentially add to the previous body of literature by using MRSA-specific lab data.

Objective 2: Determine the direct and indirect costs of SSTIs and MRSA-associated SSTIs among active duty Army trainees while in training using a cost of illness framework.

Specific Aim 1: Estimate the direct medical (clinic, hospital, and lab) and lost productivity costs (lost duty days from disposition) associated with SSTI and MRSA-associated SSTI by conducting a cost of illness (COI) study.

Specific Aim 2: Measure the association between costs of SSTI and predictor variables (disease status, demographic characteristics, hospitalization, antibiotic use) through univariate and multivariate analyses.

Significance: The estimates attained from this analysis will be used in developing a decision analytic model to assess the cost-effectiveness of a personal-hygiene based prevention strategy against SSTI and MRSA-SSTI in an active duty military trainee population.

Objective 3: Systematically review the medical literature to qualitatively and quantitatively synthesize (1) the spectrum of community-based hygiene preventive methods available to prevent SSTI or communicable infections with similar transmission mechanisms such as person-to-person skin contact exposure and (2) the effectiveness of different hygiene-based preventive methods (i.e. antiseptic wash or wipe, hand hygiene, hygiene education, and disinfection) in prevention of SSTI and similar infections.

- *Specific Aim 1*: Conduct a systematic review of the literature that will yield the following:
    - Descriptive assessment of the distribution of community-based hygiene studies based on recommendations provided by public health organizations.
    - Estimate of individual study effect size of hygiene practices' on rates of communicable illness like SSTI
    - Summary estimate of effect size of hygiene practices on rates of communicable illness using a DerSimonian Laird random effects model
    - Description of sources of heterogeneity among prevention trials
    - Assessment of statistical heterogeneity around the pooled-estimate

- Sensitivity analysis by type of study (RCT vs. Non-RCT), study quality (met quality criteria vs. not meeting criteria), and potential confounding variables (age, gender, type of community).

Significance: Conducting a systematic review is important for estimating the effects of community-based hygiene practices on prevention of infections. Effect size estimates generated by the review will be used in cost-effectiveness model.

Objective 4*:* Evaluate the cost-effectiveness of an enhanced multi-component hygiene-based intervention for SSTI prevention among active duty Army trainees.

Specific Aim 1: Perform a cost-effectiveness analysis (CEA) using a decision analytic framework to estimate the costs and effects associated with the individual and combined components of hygiene-based prevention strategy using direct estimates from the Fort Benning trial and information from objectives 1 through 3.

Specific Aim 2: Simulate cost-effectiveness of individual and combined components of a hygiene-based prevention strategy using varying probability distributions using Monte Carlo simulation techniques.

Specific Aim 3: Conduct a sensitivity analysis to assess the impact of disease prevalence, population characteristics (age and gender), and hygiene method used, on the incremental cost-effectiveness ratio using Monte Carlo simulation techniques.

Significance: To directly compare cost-effectiveness of a personal hygiene-based prevention strategy's individual components aimed at reducing SSTI and MRSA-associated SSTI.

Upon completion of the study, the overall product will include information on incremental cost-effectiveness ratios that can potentially guide SSTI and MRSA-SSTI

prevention policy not only at the DOD level, but in other high incidence community populations such as among athletic teams or prisoners.

GENERAL STUDY METHODS OVERVIEW

This study consists of four main objectives as outlined above. The first three objectives pertain to the necessary data to inform completion of objective 4 which supports the overall thesis aim (**Figure 2**). Although the objectives stand alone on paper, each one provides information necessary for the overall end product, the cost effectiveness analysis (CEA). A CEA requires several key features to be performed such as a health intervention, competing alternative, health states, health status, cost estimates, effectiveness estimates, and the incremental cost-effectiveness ratio (ICER). The choices made regarding each of these elements are driven by the CEA's perspective, which will be described in detail later. Estimates derived from objective 1 through objective 3 can and will provide information for the key features. Objective 1, the burden of illness study, provides information on health states and health status. Cost measures will be obtained from Objective 2's cost of illness study. The systematic review in objective 3 will provide information on health interventions', such as hand hygiene and community education, effects on health outcomes (illnesses prevented). Combined, all the objectives can be used to simulate an evidence-based CEA. See study pyramid below for an illustrative example of the study objectives' interconnectedness.

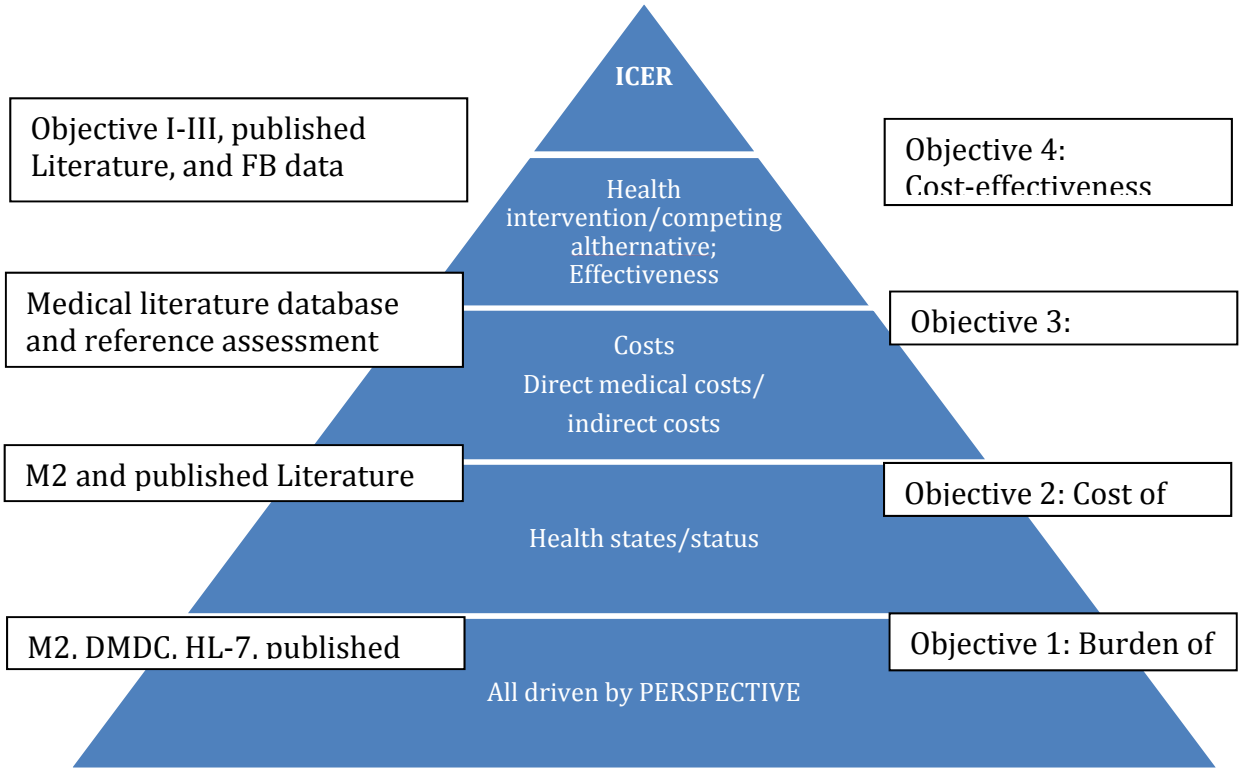


Figure 2: Study design pyramid

OBJECTIVES' METHODS AND DESIGN

Objective 1: Burden of Illness

The purpose of this study is to derive an estimate of SSTI and MRSA-associated SSTI burden on the active duty military training population (i.e. number, distribution, and trend of cases) and the military health care system (i.e. hospitalizations and antibiotics prescribed). This study will also assess potential predictors of disease.

Study Design

To determine the extent to which the active duty military recruit training components' are affected by SSTI and MRSA-associated SSTI, a retrospective, descriptive analysis will be carried out through the use of existing military health data obtained from multiple data sources (described in more detail in the "data sources" section). Through the study, information can be gleaned about the burden of SSTI and MRSA-associated SSTI in the study population. The study will evaluate the distribution and trends of SSTI and MRSA-associated SSTI among active duty military trainees visiting military treatment facilities (MTFs) from 2006 through 2009. Additionally, monthly, annual, and seasonal trends of healthcare utilization will be evaluated such as follow-up for outpatient medical encounters, hospital admissions, medical procedures and antibiotics prescribed among SSTI cases during the study period. Furthermore, the collection of disposition information can provide insight as to the recruit's lost-time in training due to limited duty days or days in quarters from SSTI or MRSA-associated SSTI.

Study Population

The study population will be drawn from those individuals who have personnel and medical records in the Military Health System's Defense Enrollment and Eligibility Reporting System (DEERS), Medical Data Repository (MDR), and Defense Manpower Data Center (DMDC). These data sources will be described in more detail in the following "data sources" section. Active duty military personnel should have a record in the Defense Eligibility and Enrollment Reporting System if they are eligible to received medical services through the Military Health System. The selected population will include those service members with a DEERS personnel record that shows a treatment DMIS ID corresponding with one of the five Army recruit training facilities (Fort Benning, Fort Jackson, Fort Knox, Fort Leonard Wood, and Fort Sill). A detailed variable data dictionary contains this information (Data Dictionary Spreadsheet, not included). Additionally, service members must be active component Army-which is indicated by the family member prefix (FMP) and the sponsor service variables. Last service members' ages should range from 17-42. All active duty military services members seen at treatment facilities described above will be included. The study population will be further separated into Army trainee and Army non-trainee subgroups (**Appendix D**). Army unit identification codes (UIC), provided by DEERS and TRADOCC, will be used to distinguish trainees from non-trainees. UIC code descriptors were only available for Army; therefore, trainee vs. non-trainee distinctions can only be made for Army.

Case definition

SSTI cases will be defined by ICD-9-CM codes 680-686.6 which are categorized under "Diseases of the Skin and Subcutaneous Tissue" as well as codes for potential

complications of infection (Bacteremia, Septicemia, osteomyelitis, endocarditis) (**Appendix E**).These codes include: 680-680.0 “carbuncle and furuncle”; 681-682.9 “cellulitis and abscess”; and 038.1 “staphylococcal septicemia”, etc. An initial SSTI case is defined as the first instance of an SSTI diagnosis. The primary diagnosis will be thoroughly evaluated 30 days prior to initial diagnosis and 30 days after initial diagnosis to assess whether the case is new or if it is a follow-on case. A new case will be diagnosis of SSTI on a new body location and separated in time (30 days). Cases will be considered as “follow-up” if the same diagnosis is observed within the 30 day window. Hospital admissions for SSTI are only of interest if the case was admitted 48 hours following the initial diagnosis. This study is particularly interested in community acquired infections as opposed to hospital acquired infections. Persons will be identified as having MRSA if they meet the following criteria (1) have a *S. aureus* culture confirmed positive and (2) confirmed resistance towards oxacillin. Persons will be matched with available microbiologic cultures based on the type of culture that was done and the date of culture. Additionally, pharmacy data will be matched based on diagnosis and culture dates (within 10 days of the diagnosis and culture). These methods have been used in previous studies using the data sources that will be used in this study.(46; 144)

Isolate classification

Isolates are classified based on methods used by the Navy and Marine Corps Public Health Center. Records of bacterial isolate in the HL7- microbiology data which have a collection date that is 10 or fewer days before or after the SSTI visit date from the SADR file will be kept for analyses. Assurance of the isolate’s relation to the SSTI is based on the specimen name and code. (46)

Data Sources

Data will be supplied from the US Army Public Health Command-Provisional (USAPHC-Provisional) and the Navy and Marine Corps Public Health Center (NMCPHC). Datasets will be retrieved from the Military Health System (MHS) Mart (M2) and Defense Health Services System (DHSS) Health Level 7 (HL7) (**Figure 3 and Figure 4**). The M2 data mart is a decision making tool that is a subset of the MHS Data Repository (MDR). M2 contains many data files from the Defense Eligibility and Enrollment Reporting System (DEERS), Standard Ambulatory Data Record (SADR), Standard Inpatient Data Record (SIDR), lab orders, and Pharmacy Data Transaction Service (PDTS). The data included in M2 are detailed, granular and used for ad-hoc queries. The data files within M2 contain similar and unique variables. HL7 is a standard messaging format for the transmission of health related data and is used for the transmission of laboratory, pharmacy, and anatomic pathology data that originate with records entered into each fixed Military Treatment Facility's (MTF) CHCS system. These data sources were chosen because the information from each system is derived from a central data source (i.e. MDR) which will decrease the variability between datasets in future analyses. Also the use of the M2 system is more appropriate for future cost-of-illness and cost-effectiveness analysis studies as it has information on costs, unlike other systems such as DMSS.

Population summary data from DEERS will be used to determine the monthly population for active duty recruits during the study period and will serve as the denominator for cumulative incidence calculations. M2 data will be used to acquire outpatient and inpatient information on active duty recruits presenting to their MTF for an SSTI. M2 data will also provide information on population characteristics, healthcare

utilization (clinic encounters, hospitalizations, clinical management, etc.), and information on patient disposition such as being sick in quarters or having limited duty (**Figure 4**). M2 also provides costs information (shown in later sections) that will be used in the cost of illness and cost-effectiveness analysis objectives. PDTS will be used to gain information about the type, amount, and costs of prescribed therapeutic regimens for SSTI and MRSA-associated SSTI (**Figure 4**). HL7 will be used to identify microbiologic results of SSTIs that were cultured for *Staphylococcus aureus* and antibiotic susceptibility information (**Figure 4**).

Last, Defense Manpower Data Center (DMDC) datasets include service-member arrival and departure dates which will provide person-time estimates for incidence density calculations. The USAPHC-Provisional can only provide Army level DMDC data (**Figure 4**).

The primary difference between the Defense Medical Surveillance System (DMSS) and the Military Health System Mart (M2) data systems is DMSS is a surveillance system and M2 is a decision making tool that includes data from multiple sources through the MHS Data Repository (MDR). See figures below for an example. The MDR receives feeds from CHCS, DEERs, PDTS, and other systems. The MDR then batches weekly or monthly reports to the M2 system. M2 appears to be the more appropriate dataset to use for both determining the burden of SSTI and cost of SSTI in the recruit population. Demographic, enrollment, cost, and diagnostic variables are included in the M2 system. Further, links can be made between M2 data and CHCS outpatient laboratory data. The system provides information on all services and since it

includes information a UIS code, military trainees can be distinguished from non-trainees.

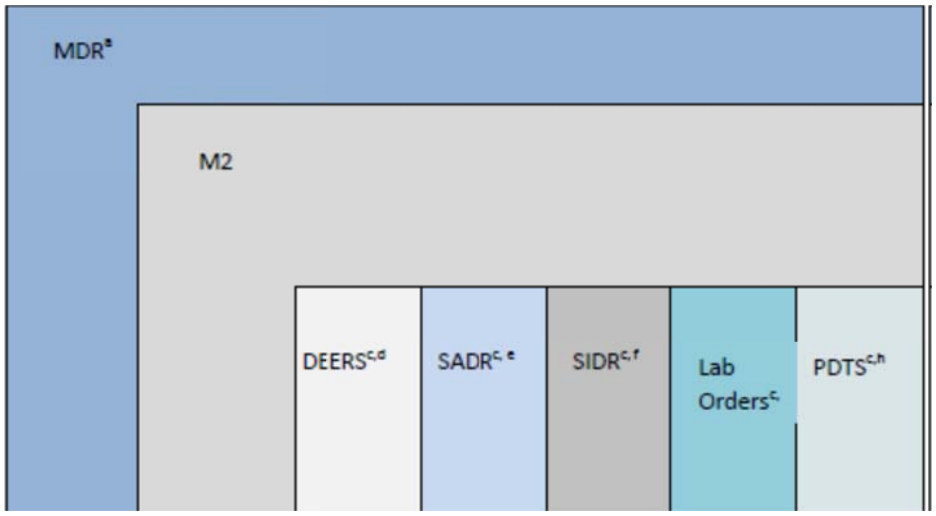


Figure 3: Data sources
[a] Data from multiple data systems feed into the MDR (i.e., Composite Health care System (CHCS),AHLTA, DEERS, PDTS, and Purchased Care).[b] Data are batched and fed into MDR processing and Storage System on a weekly/monthly basis. Through M2, users can access these data feeds through queries. [c] Data can be retrieved by building a query based on the files selected within the DEERS, SADR, SIDR, Ancillary Lab, and PDTS "business objects" folders [d] Defense Eligibility and Enrollment Reporting System (DEERS)[e] Standard Ambulatory Data Record (SADR); data source-AHLTA [f] Standard Inpatient Data Record (SIDR); data source-CHCS [g] Pharmacy Data Transaction Service (PDTS)

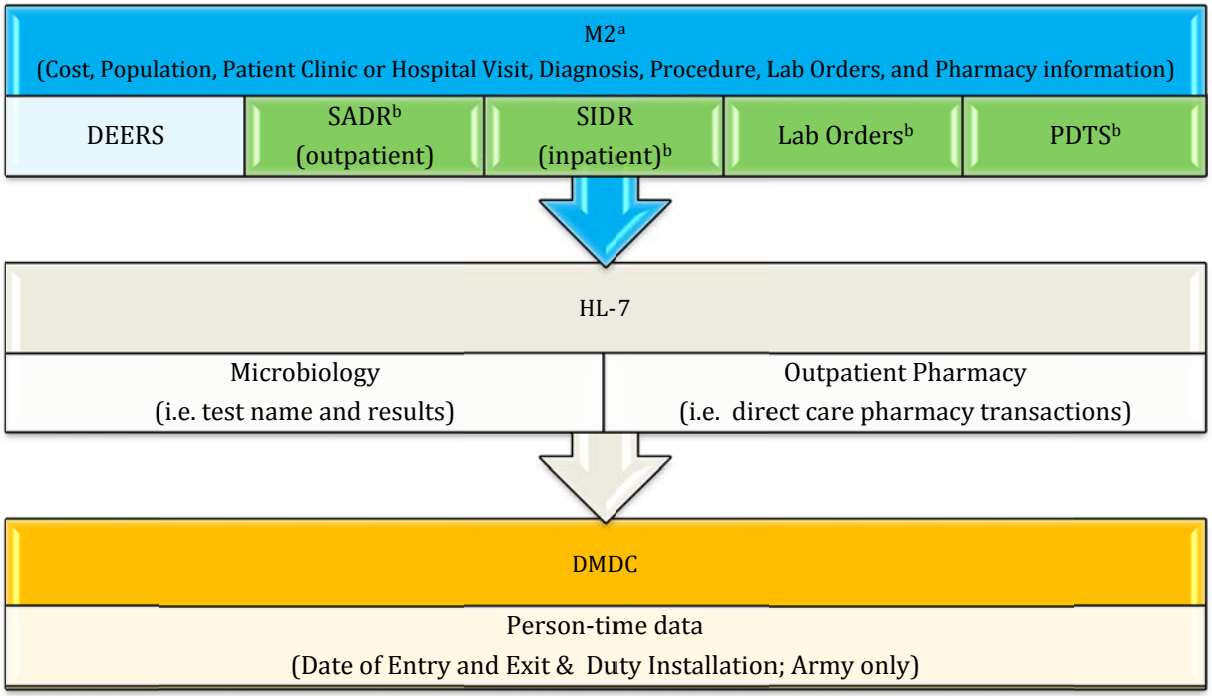


Figure 4: Data source flowchart
[a] To view all variables from these data sources, please see Appendices and attached Data Dictionary Spreadsheet [b] These datasets within M2 have sources of cost information see Table.[c] M2, HL-7, and DMDC datasets will be merged by Army Public Health Command Personnel based on unique identifiers; principal investigator will be provided a de-identified dataset.

Statistical Analysis

Study measures

Burden of disease can be measured in many forms such as the number of visits for an illness and incidence-density rates of clinical and hospital encounters because of disease, and lost duty time from being sick in quarters or a limited duty disposition. In this analysis, burden outcomes will be based on three main categories: (1) clinical outpatient care; (2) hospital care; and (3) lost-time in training. For the first two categories, burden will be measured by assessing the number of visits (initial and follow-up), monthly, annual, and seasonal incidence density rate of clinical or hospital

encounters for SSTI and MRSA-associated SSTI (**Figure 5**). Incidence density will be measured as incident cases (visits) per 1,000 person years.

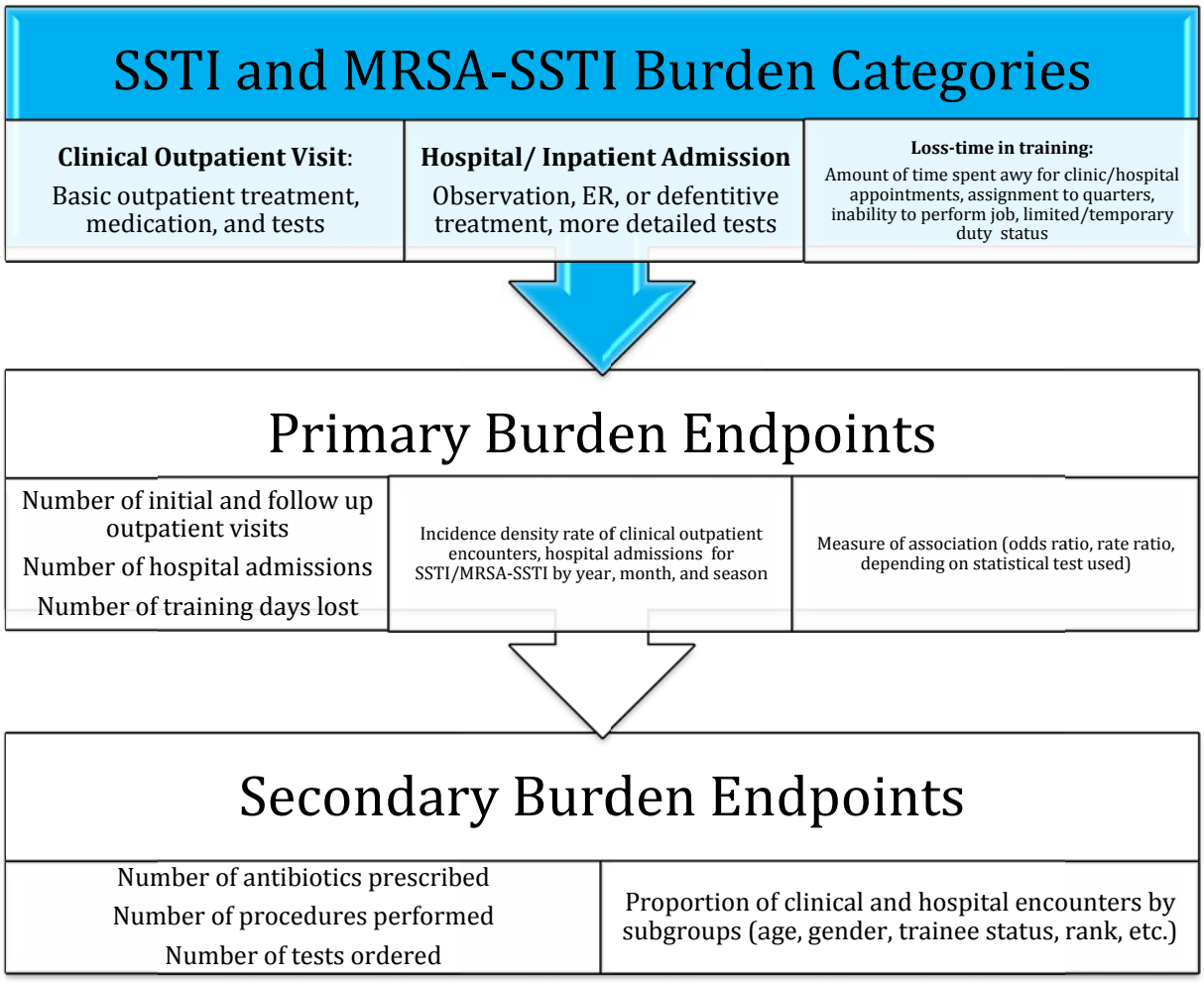


Figure 5 Burden of illness categories and endpoints

Lost-time in training burden will be assessed by using methods established by the Army Health Hazard Assessment Program's Medical Cost Avoidance Model (1). A description and assumptions of the model are described in the subsequent *Cost-of-Illness* section. Lost-time burden will be assessed by calculating the incidence of limited duty and sick-in-quarters assignments for SSTI or MRSA-associated SSTI (annotated by "disposition" variable), clinic visits, hospital visits and the duration of hospital stay.

Then the measures will be added together to generate a lost-time variable. Calculations are provided in **appendix F**. All the outcome measures obtained through this objective will be used to estimate cost-of-illness in additional analyses.

Data sources to obtain information for each of these measures are described below. Briefly, outpatient and inpatient information on SSTI diagnoses or medical procedures (e.g. incision and drainage) is captured in SADR and SIDR, respectively. The "Lab Orders" and PDTS data sources provide the number of wound culture orders or prescribed antibiotics for a clinic or hospital encounter. Lost-time in training is measured by the number of days missed because of disposition (i.e. limited duty profile or sick in quarters) and length of stay if admitted to the hospital.

Potential predictors of burden outcomes will also be assessed. The main predictor of interest is training status as this study is interested in the burden of SSTI, specifically MRSA-associated SSTI, in the trainee population. Other potential predictors are age, gender, ethnicity, rank, sponsor status, assigned duty location, MRSA infection, and year. Potential confounders include age, gender, and seasonal variation. Studies have noted previously that younger males had a higher risk of infection.(38; 216) Most predictor variables are categorical except for age, length of stay, number of visits, and number of antibiotics prescribed. All information for these variables is in the data sources described in **Figure 5**.

All analyses will be done using STATA 11.0. Descriptive analyses will be performed to measure the distribution and trends of the three burden categories (clinic, hospital care and lost-time) and disease outcome on study population characteristics (age, sex, training, site, rank, ethnicity, etc.). Case demographics will be restricted to the first

initial case. For categorical variables (e.g. sex, ethnicity, marital status, pay grade, rank, service, trainee status) incidence and relative frequencies will be calculated. For continuous variables (e.g. age, number of clinic visits, number of hospital visits, length of stay, number of antibiotics prescribed) descriptive statistics including mean, median, standard deviation, and inter-quartile range, will be measured. Annual and seasonal trends in SSTI incidence will also be evaluated. Incidence density rates of SSTI and MRSA-associated SSTI will be calculated as number of cases per 1,000 person years. Odds ratios will be calculated to measure the degree of the association between population characteristics and individual burden categories. Mantel-Haenszel (M-H) Odds Ratios (OR) will be calculated in univariate stratified analysis to adjust for potential confounding variables (age and sex). Mean differences of age, number of clinic and hospital visits, number of antibiotics prescribed by trainee status will also be calculated.

To measure differences between the binary outcome (e.g. SSTI, yes/no or MRSA, yes/no) and categorical variables (trainee status, gender, rank, ethnicity, year, season, etc.) $\chi 2$ test will be used. Mantel-Haenszel $\chi 2$ test will be used to control for potential confounding by the gender variable. To measure the differences between outcome and continuous variables (age, number of clinic procedures, length of stay, number of prescribed antibiotics) Student t-test will be used. All tests will be considered significant at $\alpha<0.05$; 95% confidence intervals (CI) will also be generated.

Univariate and multivariate analyses will be performed to evaluate the relationship between burden outcomes and potential predictors of outcome. The primary outcome of interest is the incidence rate of SSTI and MRSA-associated SSTI among an army trainee population. Univariate analyses will be used to evaluate if predictor

variables have an impact on the number of events (i.e. SSTI cases) that occur. Since incidence rate measures are based on count data (number of SSTI cases, number of clinic visits, etc.), the outcomes follow a Poisson distribution and a Poisson regression model can be employed to analyze the relationship between the outcomes and the predictors of interest. A Poisson regression model can be used to calculate both rates and rate ratios. The same model will be used to assess the relationship between ambulatory and hospital incidence density rates with predictor variables. Furthermore, multivariate analyses using the same regression model will be performed to control for potential confounding variables (e.g. age and gender) and to assess potential predictors of an SSTI diagnosis, SSTI outpatient visit, hospital admission, or lost-time in training. The predictors of interest are MRSA-infection and trainee status. Such techniques were used in a previous study of lower-extremity cellulitis.(134)

The Poisson model follows three main assumptions (1) the probability that event occurs during an interval is proportional to the size of the interval; (2) an infinite number of events are theoretically possible during an interval; and (3) the addition of one count does not depend on the post or present number of events. To test the models fit, the linearity assumption will be tested to ensure the effect of the predictor variables on the log of the rate is linear and the Goodness of Fit test for Poisson models will be used. It is assumed that for a Poisson variable the mean is equal to its variance. If the variation is greater than the true Poisson then over dispersion occurs; therefore, a Poisson model may not be used. An alternative method to the Poisson could be a Negative Binomial Regression.(72; 175)

Objective 2: Cost of Illness (COI)

The purpose of this objective is to estimate the direct medical and lost productivity costs of SSTI and MRSA-associated SSTI in the active duty military trainee population compared to the non-trainee population. Cost estimates will be generated through a COI framework. These estimates will be used in a subsequent cost-effectiveness analysis. Direct-medical and indirect costs will serve as baseline information for current standard of care for SSTI and MRSA-associated SSTI within the military health system.

This is the first study to estimate direct-medical and indirect costs of SSTI among active duty military trainee populations. Since direct medical cost data will be coming from a central data source (M2) that includes ambulatory and hospital data, better delineations can be made between outpatients and inpatients. This will be the first instance of using comprehensive military medical data system that reaches multiple MTFs across the United States, so analysis will not just be limited to a single hospital or training installation. Additionally, the cost of SSTI in terms of lost-productivity will be assessed along with hospital and clinic costs, which may yield valuable information for training commands.

Knowing the costs can potentially change policy by making recommendations about how to best allocate resources with respect to SSTI and MRSA-associated SSTI in the training environment. Furthermore, knowledge gained about the active duty trainee population can potentially be applied to similar deployed and operational settings. A COI study can also provide more information regarding the SSTI burden in the active duty recruit training population. Last, estimates generated through this objective will provide a baseline for subsequent cost-effectiveness analysis of prevention efforts.

COI Framework

A retrospective COI evaluation will be performed to analyze the direct medical and indirect costs incurred from diagnoses of SSTI and MRSA-associated SSTI among the active duty military trainee population. The **incidence-based method** (IBM), which calculates the value of lifetime costs for new cases of disease or illness, will be used which will provide information about the cost of averting a case**.** Use of this approach will allow for the cost of SSTI to be measured from onset to conclusion for SSTI cases beginning within the period of study (2006-2009). According to Segel (2006), the incidence-based method is essential for calculating the value of prevention. The IBM has its limitations as it requires more data and it makes assumptions regarding lifetime costs. Although these limitations exist, methods are available to approximate lifetime costs if necessary such as modeling a synthetic cohort of people with SSTI over time.(33; 115; 177)

Study characteristics

Study Population

The study population used in this analysis is the same as the population described in objective one. Briefly, all Army active duty military training personnel, ages 17-41, receiving care at a military treatment facility from calendar year 2006 through calendar year 2009, and assigned to one of five Army recruit training facilities will be considered for inclusion in the study.

Medical resources

Medical resources include personnel, treatment, and testing sources. Physicians, nurses and laboratory workers are considered personnel involved in the treatment and

testing of patients. Treatment often involves wound care or antimicrobial prescriptions. Testing includes microbiologic test of wound cultures for antibiotic susceptibility. All resources used within one year from the initial diagnosis of SSTI will be considered for inclusion in the study.

Audience and Perspective of the analysis

This study will be done from a military healthcare system perspective. Although using a societal perspective is considered the gold standard as it includes all costs and provides a baseline for future comparison, such a prospective is too cumbersome and beyond the scope of this study (177). Only military health data sources will be used for this COI analysis which makes the use of a military and military health system perspective more appropriate. This perspective includes only costs related to the military health care system and military (i.e. treatment and lost productivity).

Outcome measures

A medical cost-avoidance model was developed by the Army Health Hazard Assessment Program.(34) This model assumes five basic events resulting in an exposure to a health hazard clinic visit, hospital admission, loss of time away from the job, disability, and fatality. Although this model was developed for estimating injury costs, elements of the model can be used to estimate costs related to SSTI and MRSA-associated SSTI. Three model elements will be used to estimate costs in this analysis (1) clinic; (2) hospital; (3) lost-time. The other two measures of costs (disability and fatality) included in the model are beyond the scope of this study. Clinic costs include basic outpatient treatment, medication, and tests. Inpatient observation, emergency or definitive

treatment, and more detailed test comprise hospital costs. Last, clinic and hospital appointments, assignment to quarters, and limited duty are considered lost-time costs.(1)

Total cost (TC) and average cost (AC) of SSTI and MRSA-associated SSTI are the two primary outcome measures of interest. TC will be derived by calculating the overall costs for medical care and lost-time. Average costs will be calculated as total costs divided by the number of patients being treated for an SSTI.

Summary measures

Multiple summary measures will be generated and are listed below.

a. SSTI or MRSA-SSTI specific costs
b. Cost per trainee with an SSTI
c. Cost per trainee with a MRSA-associated SSTI
d. Cost per trainee with a SSTI or MRSA-associated SSTI with/without training cycle loss/recycle
e. Annual costs: COI per year

Sensitivity analyses

Much uncertainty can surround parameters in a COI assessment; therefore, a sensitivity analysis will be done to explore areas of uncertainty around cost estimates. The sensitivity analysis will show potential variation of the total, average, and annual costs based on uncertainty factors such as MRSA-infection prevalence (1-5%), seasonal variation (summer and spring vs. fall and winter), discount rates (2-4%) and time horizon variables (short term and long term horizons). All these variables can potentially influence cost estimates.

Adjustments and discount rates

The cost estimates provided in the database already adjust for inflation. Cost adjustments are based on the previous year. For more information regarding the cost estimates and their respective adjustments please see the M2 data dictionary.

Data Sources and Variables

Direct medical and indirect cost data (DMC and IDC, respectively) will be provided from data sources used in objective 1. DMC variables will be obtained from the SADR, SIDR, Lab orders, and PDTS data files; while IDC estimates will be calculated using information from the Accession Medical Standards Analysis and Research Activity (AMSARA) annual report and the Army Military-Civilian Cost System (AMCOS) Lite database (**figure 6**).

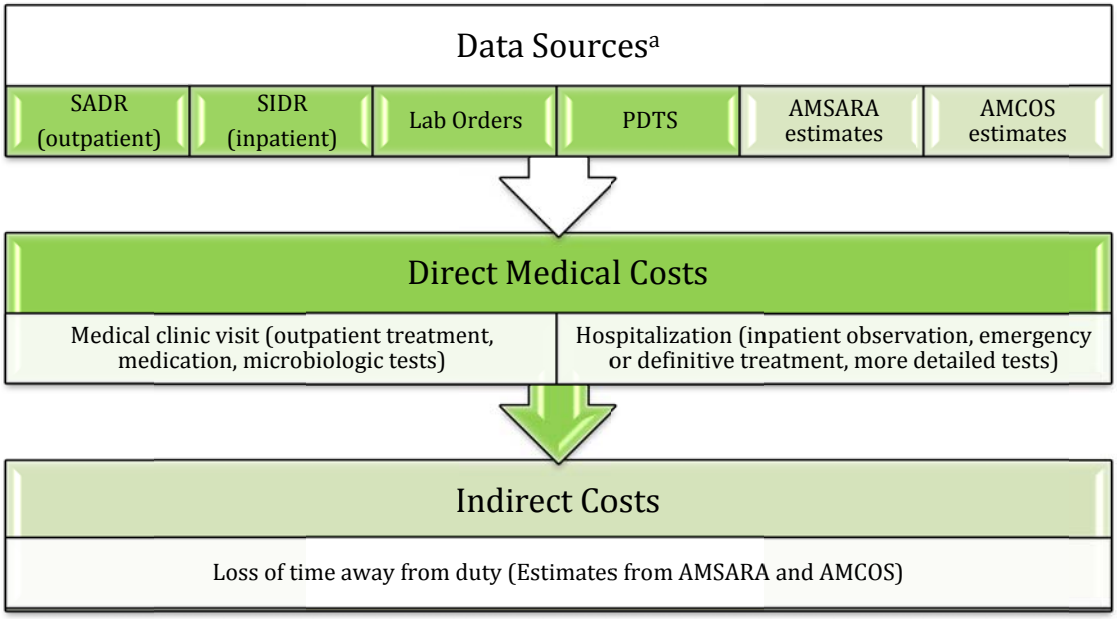


Figure 6 Data source flowchart
[a] Cost data sources obtained from M2 datasets, AMCOS, and AMSARA

SADR and SIDR contain cost estimate variables for ambulatory visits and hospitalizations, respectively. The primary variables of interest for this analysis are the full and variable cost estimates. Full cost variables are derived in SADR by adding ambulatory patient group (APG) costs to the Organizational Work Relative Value Unit (RVU) derived clinician salary. APG-based full cost is calculated using the Military Treatment Facility (MTF) wide average (across all work centers in the MTF) for APG full costs. Discounting is applied to this cost. Full costs are based on the prior fiscal year's Medical Expenditures Reporting System (MEPRS). Additionally, full costs are adjusted for inflation. SIDR full cost estimates are generated in a similar fashion except a completion factor is used to generate total full cost rather than a RVU. The lab orders file also contains the full and variable cost variable. The primary variable of interest in the PDTS file is the full cost-allowable amount. Ingredient cost, dispensing fees, and taxes, regardless of source system are factored into the pharmacy cost.

AMSARA generates annual reports with estimates on hospitalization and attrition by disease (159). This information could be used to assess productivity losses from SSTI. The AMCOS database was used in a previous injury cost avoidance model to estimate productivity losses. This tool can be used to determine the cost associated with personnel as it contains a comprehensive file of personnel-related cost factors such as basic pay rates, military procurement, and operation and maintenance costs (1).

Information on predictor variables will also be obtained from M2 (SSTI incidence, MRSA prevalence, sex, age, training status, season, etc.). This information has been described previously in objective one.

Analysis plan

Study measures

As stated before the total cost (TC) and average cost (AC) related to SSTI and MRSA-associated SSTI in the active duty military training population are the outcomes of interest in this objective. Detailed cost calculations are provided below. These calculations are based on guidelines from the Centers for Disease Control (CDC)'s Economic Impact Module and the Army Cost Avoidance Model (CAM).(1; 33; 34; 115) Total cost includes costs of medical resources to treat disease (clinic and hospital costs), non-medical resources, and loss in productivity (sick in quarters or limited duty time). For the purposes of this study, non-medical costs (e.g. child care and travel expenses) will not be included as this information is not available. Although TC is useful for measuring the costs of treating a disease, TC is an aggregated measure and can be difficult to interpret. Additionally, it is not easy to use when comparing programs with different outcomes. Using AC will allow for comparisons to be made in future CEA and

in subgroup analyses. The AC is defined as the cost per patient treated (calculations are provided in **appendix G**).

Predictor variables described and assessed in the burden of illness objective will be used. These variables have been described in previous sections but to summarize the variables are grouped into three major categories (1) population characteristics; (2) clinic visit; and (3) hospital visit information.

Descriptive analysis

All analyses will be done using STATA 11.0. Basic descriptive statistics (i.e. mean, median, and standard deviation) will be computed for all cost variables included in the dataset. Sum of costs across predictor categories (age, sex, trainee status, etc.) will also be calculated. Clinic, hospital, and lost-productivity costs estimates will be calculated based on the previously described cost avoidance model (CAM) and guidance from the CDC's economic evaluations tutorials.(1; 33; 34; 115) The cost calculations have also been modified to fit the scope of this COI analysis. The CAM includes probabilities for hazard exposures which will not be assessed in this study. But CAM generates cost estimates with similar methods recommended by the CDC's economic tutorial as illustrated in the equations provided in **appendix G.**(33)

Inferential Analysis

Univariate cost analysis will be performed to assess the differences in total costs and average cost among baseline characteristics (age, sex, rank, trainee status, MRSA-infection). The statistical method used is dependent on the data variable type and the distribution of the cost data (e.g. nominal vs. continuous; normal vs. non-normal). All test for significance will be two-tailed with α=0.05. Cost endpoints will be evaluated for a

normal distribution using the skewness and kurtosis test for normality (skew test) (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP). The skew test is being used as opposed to the Shapiro Wilk test used in previous studies (111) because Stata does not limit the number of observations entered with this method. If the normality assumption holds, then parametric analytic methods will be employed (Student's t). Conversely, if cost data are assessed as non-normal two steps will be taken. First, a log-transformation of cost data will be performed to approximate a normal distribution. Cost data tend to be skewed to the right, taking a log of the cost can make the distribution approximately normal. If severe kurtosis of the cost data occurs, then non-parametric Wilcoxon rank sum test (an analogue to the t-test) will be used instead as log-transformation would not be appropriate.(111; 199)

Multivariate cost analyses will be performed to determine potential predictors of costs as well as account for potential confounding variables (age, sex). A generalized linear model (GLM) using a log link function will be used to perform this analysis, if the assumption of a reasonable distribution can be maintained. GLM commands give large degrees of flexibility in the choice of each of the features of the model.(199) This model allows the analysis to be tailored to the data rather than having to transform or otherwise manipulate the data to fit the analysis. Previous cost-of-illness studies have used generalized linear models (GLM) with a negative binomial distribution and a log-link function for multivariate regression analyses to determine predictors of costs.(129; 136) In cases where substantial kurtosis exists among the log of the cost, GLM would not be used as precision could be inadequate. In this case, a semi-logarithmic ordinary least squares model, with the natural log of total costs can be used. Filice et al used this

approach when faced with a similar issue in assessing predictors of healthcare costs.(70) An example of the model can be found in **appendix F**.

If clustering of data occurs, a generalized estimating equation (GEE) will be applied. Menzin et al. noted that clustering of data can occur among patients treated at the same facility because they will receive the same standard of care compared to other facilities.(136) Although the active duty military training population is receiving care under the military health care system, standard of care could be different from one MTF to another.

Sensitivity analysis

Sensitivity analyses will be performed for two main reasons (1) assessing model fit and (2) to evaluate the effects of parameters such as MRSA-prevalence, discount rates, seasonal variation, and time horizons on cost estimates. The relationship of the mean to the variance will be assessed by using residual plots and plots of subgroup stand deviations versus the mean.(199)

One-way sensitivity analysis (OSA) will be used to evaluate the effects of parameters surrounding cost estimates. OSA assumes that the predictor variables are independent of one another. To control for possible confounding, multi-way analysis will also be performed. This analysis will assess the effects of all the four predictor variables listed above on the cost estimates.

Approaches to handling missing data

If a large number of cost estimates equal $0, a gamma distribution can be assumed. This distribution can be used for positive continuous variables that incorporate the assumption that standard deviations are proportional to the mean.(199)

MEPRS outpatient cost information will only be captured in M2 if the MEPRS code begins with a "B", which is an ambulatory visit designator. MEPRS codes beginning with any other letter will have a value of $0 because their costs are captured by other clinics, which can underestimate the average costs per outcome of interest. These will be estimated as missing values rather than $0.(1)

Objective 3: Systematic Review

Purpose

This objective's purpose is to qualitatively and quantitatively evaluate hygiene-based methods' effect on prevention of communicable infections, like SSTI, using comprehensive, systematic, methodology. Guidance published by multiple organizations recommends instituting hygiene-based practices like, use of antimicrobial agents to sanitize hands, hand washing and showering, hand hygiene education, and environmental decontamination, to prevent MRSA-infections. Although this guidance has been issued, the literature lacks a systematic evaluation of the effectiveness of these practices on communicable infections, like SSTI. Multiple systematic reviews have been done to evaluate individual hygiene measures' effects on communicable illnesses but have not evaluated the overall effect of these measures. This review will attempt to provide an estimate of the effect size of personal-hygiene based practices on communicable illnesses, like SSTI.

Additionally, estimates of effect size will be used in subsequent cost-effectiveness analysis (CEA). Systematic reviews of the literature are often done to obtain such effectiveness measures when actual trial data is unavailable.(62) A number of CEA studies have performed systematic reviews and produced an estimate used in hypothetical models, especially with regards to CEA of universal screening measures for MRSA or hand hygiene compliance.(52; 119)

Method and design

The structure of this sytematic reivew is based on guidance provided by Egger's, *Systematic Reviews in Health Care: Meta-analysis in context*. The approach suggested by Egger includes 8 steps (1) formulating the review question; (2) defining inclusion and exclusion criteria; (3) developing a search strategy; (4) selecting eligible studies; (5) study quality assessment; (6) data extraction; (7) analyses; (8) interpretation of the results. The methods outlined by Egger are widely used in systematic reviews of the health care literature like those assessing effectiveness of hygiene practices.(49; 57; 62; 135; 205)

Inclusion and Exclusion criteria

Participants

Studies that include men, women, and children involved in hygiene-based measures to prevent a communicable infection. The participant inclusion criteria is based on previous systematic reviews of the literature in this area and will broaden the amount of information available for the review.(5; 6; 49; 53; 135; 205)

Interventions and comparisons

Interventions of interest for this review include hygiene measures recommended in guidance previously mentioned in the background section. These measures include the following components:

(1) Use of an antiseptic solution or wipes for washing hands or showering (like chlorhexidine)
(2) Hand hygiene program
- Hand washing with soap and water
- Hand washing with antimicrobial soap and water
- Alcohol based hand sanitizer

(3) Hygiene education program
- Consists of infection control and hygine overview, pictures, stories, posters, etc. Definition of hygiene education program based on previous literature review criteria(5). Must indicate a systematic provision of education in the intervention group but not in the control group.

(4) Disinfection measures
- Use on an EPA approved agent to reduce microbial contamination

Outcomes

Studies will be considered for inclusion if they report the following outcomes.

Communicable illness infections or symptoms:
- Skin and soft tissue infections (cellulitis, abscess, boils, carbuncles, furuncles, etc.)
- MRSA related infections (SSTI, pneumonia, etc.)
- GI infections (diarrhea.)
- RI infections (URI, LRI, ILI, pharyngitis)
- Combination of outcomes

The primary measures of interest include rates of infection, percent reductions in infections, odds ratio. Secondary measures include mortality, abseteeism, and length of hospital stay as surrogates for method effectiveness.

Study design and methodological quality

Randomized controlled trials (RCTs) and non-RCTs as well as observational studies (i.e. prospective and retrospective cohorts, case-control, and pre-post test studies)

will be considered for review. Case reports and case series will be excluded from the study. RCTs often provide the best evidence of an interventions efficacy (62), but are often lacking in the prevention literature. Although observational studies are prone to bias, confounding, and overestimation of effect size (62), they are important to include because RCTs are not always ethically possible to conduct when evaluating preventive measures. The important aspect to remember when including observational studies in the review is to account for these differences in the studies when assessing study quality and performing analyses (described in sections IV and VI).

A study's analytic methods should be clearly stated in the article to be considered for inclusion into the review. Measures provided should at least include descriptive calculations (percent reduction, incidence or prevalence, mean, and stand deviation) and point estimates (prevalence or incidence rate, odds ratio, or risk ratio) along with 95% confidence intervals (if available). Analytic techniques, such as univariate or multivariate regression, should be described.

Search strategy

Search strategies and terms are based on methods described in peer-reviewed literature of hygiene practices.(5; 49; 53; 121; 205) Searches of major electronic clinical trials and peer-reviewed literature databases (**Box 1**) from 1980 through 2010 will be conducted using search terms listed below (**Box 2**).The search will start out broad and then become more narrowed based on variations of the search terms. Search term strategies have been provided in previous studies.(5) The primary terms this search will include relate to the infection (e.g. infecitous disease, SSTI, RI, GI)and the prevention measures (e.g. chlorhexidine, antibacterial soap, education, etc). Search results will be

examined for pertinent articles and systematic reviews as well as reference lists to search for additional articles. Only English language articles will be used in the this review due to limited fiscal resources. Guidance is mixed as to whether to include non-English language reports, as exclusion could be a potential source of bias. As such, it should be noted when reporting the results of this review.(62) Results of studies obtained from this search strategy will be presented in a flowchart.

Box 1
Data Sources

- *The Cochrane Clinical Trials Register*
- *Cochrane Review Library*
- MEDLINE
- EMBASE
- Cumulative Index of Nursing and Allied Health Literature (CINAHL)
- Conference proceedings like IDSA or SHEA
- Sources of ongoing and/or unpublished studies
- Reference lists

Box2

Example of Keyword Search Terms

- Skin infections
- Cellulitis
- Abscess
- Methicillin-resistance
- Oxacillin-resistance
- *Staphylococcus aureus*
- Staphylococcal infections
- Penicillin resistance
- Primary prevention
- Education
- Chlorhexidine
- Decolonization
- Surveillance
- Infection control
- Communicable disease control
- Community, Military personnel, Athletes, Sports teams, Prisoners, Inmates
- Hygiene
- Disinfection
- Antimicrobial agent

Study selection

All relevant citiations, titles and abstracts meeting the inclusion criteria will be imported into a reference database where duplicates will be manually removed. Titles and abstracts will be retrieved by one reviewer but will be evaluated by two reviewers. Selected studies will be independently evaluated by two reviewers. Use of more than one reviewer is preferred to minimize errors and to resolve issues regarding subjectivitiy.(62) A consensus method of open discussion will be employed to resolve disagreements. If the two reviewers cannot come to a consensus, a third reviewer will be used for further study evaluation. Such methods have been employed in similar studies.(135; 205)

Excluded studys' information (i.e. author, title, journal, year, intervention, and reason for exclusion)will be kept in an exclusion log (**Appendix H**).

Quality assessment

Assessment of study quality is necessary to determine potential sources of error around the estimate, bias and confounding. The effect size obtained from a study is only as good as the study quality. The effect size can be overinflated or underestimated depending on the type of error. Both RCTs and non-RCTs of hygiene practices will be included in this review; therefore, it is recommended to use a quality assessment tool that includes metrics for both types of studies. Many tools are avialable, but the widely used tool, Jadad's scale, which evaluates randomization, blinding, withdrawls, and dropouts(57; 91; 128; 201) does not capture elements of bias and confounding often found in non-RCTs. A tool that has been partially validated, created by Downs and Black (1998), can be used to assess study quality of both randomized and non-randomized studies.(60) A systematic review of tools used to evaluate the quality of non-RCTs (57)

found this tool to be one of the best tools that would be useful in a systematic review. Furthermore, it not only is a partially validated tool, it is one of the only tools that has been developed to evaluate both the quality of RCTs and non-RCTs. (57) The tool consists of 27 items to measure study quality, split into four sections: reporting, external validity, internal validity-bias, and internal validity-confounding. A caveat to using the tool is that is does not include questions related to baseline comparibility and the random allocation mechanism only pertains to randomized studies. This tool has been used in a number of studies.(45; 91; 164; 171) All studies included RCT and non-RCT designs. Of the studies noted, two modified the scale (45; 164) by dichotimizing the last question regarding sample size. The total score achievable is 24 points for observational studies and 28 points for RCTs; with 0 being the poorest quality and 24 or 28 being the best quality. Quality scores >20 are usually considered good while those with scores <11 are considered poor.(91) Scores from 11 through 20 are considered moderate.

Two independent reviewers will assess study quality.(62) The reviewers will not be blinded. Although Jadad et al found that blinding produced lower, more consistent scores; others have found that it is time consuming and the potential benefits may not always justify the additional costs.(24; 101) A consensus process, in which reviewers discuss disparities and then come to an agreement, will be used to resolve differences in quality assessments.(57)

Data extraction

Two reviewers will independently abstract data from all studies meeting the eligibility criteria. Data will be collected on a pre-printed data abstraction form and then entered into Review Manager (most recent edition). Data extracted will include

information on study design (type, duration, setting, location); participant characteristics (age, race, sex); type of intervention; illness information (case definition, symptoms, diagnosis codes, lab culture information); sample size; and if available bacterial characteristics, MRSA prevalence, andside effects. Primary and secondary outcome descriptions will be collected as well as outcome measures regarding the number of cases, odds ratio, risk ratio, and infection rates. Additonally, the abstraction form will capture information on possible sources of bias (selection of controls) or confounding. Last, the author's conclusions will be collected.

Analysis

Study characteristics

Analytic approaches are based on methods used in previous, similar, meta-analytic studies.(5; 205) All analyses will be carried out using STATA software (Meta-Analysis in Stata: An Updated Collection from the Stata Journal). Descriptive summary measures of study characteristics, percent and number or median and range, will be calculated to evaluate the distribution of studies based on study setting (location), age group, and illness outcome as well as study type (RCT or non-RCT) and quality measures (meeting study quality or not meeting study quality).

Calculating effect size

Reported risk ratio (RR), rate ratios (RR), or odds ratio (OR) along 95% Confidence Intervals (CI) will be used in analyses to estimate effect size of intervention (chlorhexidine, hand hygiene, education, and disinfection) on the outcome(SSTI, GI, RI, or combined illness). In the instance that studies do not report this information, estimates will be calculated based on information provided in the study (e.g. incidence density).

These calculations are based on previously published, validated calculations. Studies will not be included in the analysis if information is unavailable to calculate an effect size.

Estimates will be graphically displayed in a commonly used Forest plot. Ultimately, a combined effect size of hygiene practices should be gained from this review (**Figure 7**).

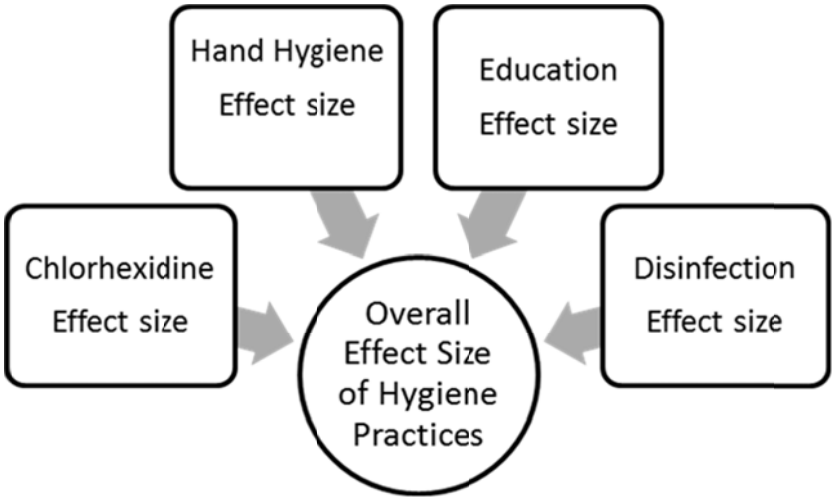


Figure 7 Individual and overall summary measures

Summary estimate of effect size calculation

If study variability is deemed low, a fixed effects model is used which assumes all studies in the analysis are functionally identical.(27) Both RCTs and non-RCTs will be evaluated in this study; therefore, we cannot assume that all studies are equal. A random-effects model will be used to perform meta-analyses and generate a summary estimate of effect size. The random effects model assumes that studies are a random sample of a population of studies in which there is variance between and with-in individual studies.(27; 62) The DerSimonian and Laird method is the most popular method for random effects modeling.(27) This is an extension of Wolfe's method, a fixed effect model, and allows for assessment for continuous and binary measures of effect (mean

difference or odds ratio). Elements needed to compute a summary effect using the random effects model include T^2 (the between study variance, the effect size, V (the within study variance), and the weighted mean.

Borenstein recommends that RCTs and non-RCTs be evaluated separately.(27) Most studies do not find it appropriate to perform meta-analyses of observational studies.(27) Pooled effects may be overestimated or the true effects of the intervention can be skewed because of the varying degree of bias and confounding within observational studies. In fact, Berlin states, "Heterogeneity is common in meta-analyses of epidemiologic data and should be viewed as the expectation, rather than the exception." (24) It is important to explore and describe sources of heterogeneity between and among studies.

If statistical synthesis is deemed inappropriate, as it may be with observational studies, a narrative review of eligible studies will be provided (**Appendices I and J**).

Assessment of heterogeneity

Once the overall summary estimate of hygiene practices effect on communicable illness outcomes is generated; the next step is to assess statistical heterogeneity around the pooled estimate. This will be done using methods described in Borenstein. A Q-statistic will be calculated along with a p-value to test for significant heterogeneity, while I^2 will be calculated to reflect the proportion of variance around the effect that is true.

If statistical synthesis is deemed inappropriate, as it may be with observational studies, a narrative review of eligible studies will be provided.

Sensitivity analysis on summary effect estiamtes

A sensitivity analysis will be performed to test for the robustness of the summary estimate derived from the meta-analyses. The stability of the measure will be tested based on tiral quality and different study designs. Furthermore, the impact of missing data on the summary effect size will be evaluated.

Reporting

Results will be reported using criteria established by both the Cochrane Handbook for Systematic Reviews and the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines.(95; 189) Randomized controlled trials and non-randomized controlled trials could meet the inclusion criteria for the proposed review; therefore, it is appropriate to use the components from each of these reporting tools. Both sets of guidelines share common elements (i.e. background, methods, results, and discussion). MOOSE guidelines are primarily concerned with potential sources of confounding and bias and what was done to control or address such sources. Observational studies often face the challenge of inherent biases and differences in study design so these issues must be accounted for when reporting meta-analyses of observational studies.(189; 198)

Objective 4: Cost-effectiveness analysis

Purpose

This objective has two purposes. First, cost-effectiveness analysis (CEA) using evidenced based information from objectives 1-3 will be done. The illness, cost, and effect information can serve two functions (1) model simulation and (2) base case analysis. Second, information obtained from the previously mentioned Fort Benning (FB) MRSA study will be used to build a model based on real world, clinical trial data. Cost-effectiveness analyses (CEA) of hygiene-based strategies to prevent SSTI and MRSA-associated SSTI in the congregate community setting, especially the active duty military trainee population, have not been performed. Through this study's analyses, average and incremental cost-effectiveness ratios will be generated to evaluate the overall costs and effects of such a program in this population.

Methods

Study framework

Audience for the study

The primary audience for this study includes DoD leadership responsible for resource allocation and prevention policy in the military training environment as well as those involved in the care and well-being of individuals in congregate community settings (e.g. preventive medicine personnel, military training personnel). Furthermore, this study is not limited to the military setting. Information gleaned from this analysis can be potentially applied to civilian settings with similar conditions (i.e. prisons).The goal of the cost-effectiveness analysis is to inform these personnel of a potentially cost-effective

hygiene strategy that can be implemented not only in a military setting but applied to similar populations.

Type of analysis

The proposed study is a cost-effectiveness analysis (CEA) which will examine the average and incremental cost-effectiveness of community-based hygiene practices on prevention of infections. Many economic analyses exist, but CEAs allow for alternative measures to be compared to a traditional form of improving health.(77; 168)Many CEAs have been done in the clinical setting; assessing the impact of empiric therapies for MRSA or universal MRSA screening to prevent transmission (30; 119), but this would be the first evidence-based evaluation of multi-component community-based hygiene practices using CEA.

Perspective of the analysis

The CEA will be performed from the military and health care system perspectives where only direct medical costs and productivity costs will be assessed. The chosen perspective drives the cost-effectiveness analysis (CEA) as it not only determines what costs and effects to count and how to value them, but it reflects the type of decisions the analysis is intended to inform.(77; 168) The Panel on Cost-Effectiveness in Health and Medicine recommends conducting a CEA from the societal prospective because it offers the broadest, comprehensive approach to CEA and is often used as the reference case. The societal prospective includes all costs and all health effects regardless of who incurs the costs and who obtains the effects.(77) The Panel recommends starting from this perspective and then drilling down to a narrower perspective. The societal perspective is not feasible with respect to this proposed study for a couple of reasons. First, this study's

perspective is limited by the type of cost data available. All cost data are derived from military health care system records. Second, the perspective relates to the overall objective of this analysis which is to inform decision makers in the military training environment and preventive medicine personnel about the cost-effectiveness of hygiene-based measures aimed toward prevention of SSTI among recruits. Ultimately, applying the findings of the proposed study to similar congregate community settings could be a future goal; but resource constraints limit this analysis to broadening to a societal perspective.

Alternatives: community-based hygiene practices to prevent infections

A number of hygiene-based methods exist and are shown in the table below. Each method will be examined in the CEA individually and in combination with one another. This CEA will incorporate hygiene-based interventions examined in objective 3's systematic review as well as hygiene-based strategies from the FB MRSA study. The impact of these practices will be modeled among active duty military ages 17-41. These strategies' aims are to prevent infection in training environments. Implementation of these measures extends the time in the training setting. For instance, trainee upon entry into training could receive education on identifying and preventing common infections and then, while in training, participate in a hygiene program that includes regular hand washing, showering with antiseptic soap after practice, and disinfection of shared surfaces (e.g. mats).

Evidence-based hygiene practices

Community-based hygiene measures can include a number of components such as hand hygiene, community-based education, and environmental disinfection. Several elements make up the components and they are described in detail.

a. Hand hygiene
   i. Regularly washing hands with plain or antimicrobial soap
   ii. Use of alcohol-based hand sanitizers
   iii. Compliance with hand-hygiene measures
b. General personal hygiene practices
   i. Access to soap and water
   ii. Adequate hygiene time for regular baths
   iii. Limit of contact and sharing of personal items
c. Chlorhexidine antiseptic body washing
   i. Once a week
   ii. Multiple times a week
d. Community-based education
   i. increases awareness of infections like SSTI
   ii. Reinforcement of good hygiene practices
e. Environmental disinfection:
   i. Disinfection with an EPA-approved cleaning agent

Fort Benning MRSA Study hygiene practices

The methods used in this study were previously described in the preliminary studies section. Briefly, group 1 will receive a basic approach that consists of a preventive medicine briefing and standardized care for SSTI; group 2 will receive the components of the basic approach plus additional hygiene education as well as be required to take a 10 minute, once weekly shower; and group 3 will receive the measures implemented in groups 1 and 2 along with an additional once weekly chlorhexidine wash.

Comparison program

Status quo: existing practice

Existing practice will be evaluated as a single comparator. It includes a combination of intervention such as incision and drainage, wound care, follow-up, and

antibiotics when needed. Using existing practice can assist in evaluating the impact of replacing the existing program with alternative hygiene-based practices.(77) Information regarding existing practice will be retrieved from the literature. This program reflects the current annual incidence of SSTI and MRSA-associated SSTI affected active duty military training populations.

Target population for the intervention

The present study focuses on strategies targeted toward persons in the United States who reside or train in congregate community populations. A number of outbreaks of SSTI and MRSA-associated SSTI in the United States have occurred in congregate community settings and have been described in previous sections of this proposal.(7; 38; 106; 216) These outbreaks tend to occur among men, who are younger (age<24) and healthier (immunocompetent, absent hospitalization and antibiotic use in previous year to infection, lack indwelling devices, etc.) and who reside or train in congregate, community populations (e.g. athletes, correctional facility inmates, and military trainees). Based on findings from previous studies, it is appropriate to further evaluate costs and effects by age subgroups stratified by gender.

Scope of the study

The study's boundaries are limited by the perspective of the study and the available data. The population is limited to active duty military service members. Although a societal perspective would encompass all populations affected by the intervention, this is not possible in this CEA. The present study's health outcome and cost data are derived from the Military Health System's (MHS) databases. Information regarding how an index patient subsequently affects family members and communities as

a whole is not available. Even if the information was available, one must consider resource limitations. Extending the CEA beyond the target population would be quite an undertaking and is beyond the intention of this objective.

Time Horizon

The present study will assess the impact of the prevention practices during two time intervals. The short-term interval is based on two factors (1) the acute nature of the infection and (2) the length of the training program. The long-term interval considers what happens after training period and the potential for recurrent infection.

Short-term horizon

Impact of the hygiene practices on prevention of SSTI and MRSA-associated SSTI will be assessed during the course of the training.

Long-term horizon

Using modeled data from estimates obtained in objectives 1 through 3; the life-time costs and effects of 1-year of the prevention program.

Analysis Plan

The proposed cost effectiveness-analysis (CEA) will use a decision analytic (DA) methodology to assess the incremental costs and effects of hygiene-based approaches to prevent SSTI and MRSA-associated SSTI in the active duty military training population. DA frameworks have been used in multiple cost-effectiveness studies regarding MRSA empiric therapy and infection control measures.(56; 119) Such a model is best suited to evaluate interventions to prevent or treat illness of a short duration like an acute infectious disease. A decision analysis model calculates the costs and effects associated

with an event in the event pathway. Additionally, DA models have been both used to simulate clinical outcomes and costs based on evidence-based literature reviews and prospective cohort data.(36; 150) Illustrations of example decision trees of the models listed below are shown in **figures 8-9**.

Conceptual models

All illustrations below are examples of the conceptual models. They are incomplete and do not reflect the full extent of the CEA. All models and analyses will be generated using decision analysis software (Tree Age Pro HealthCare Suite). Squares represent decisions along the pathway; circles are chance nodes and squares with circles are terminal nodes. The first figure represents the use of prevention strategies and the probability of developing an SSTI after their use. The second figure represents the clinical pathway an individual would follow upon development of an SSTI. The cost and effects are entered for each pathway.

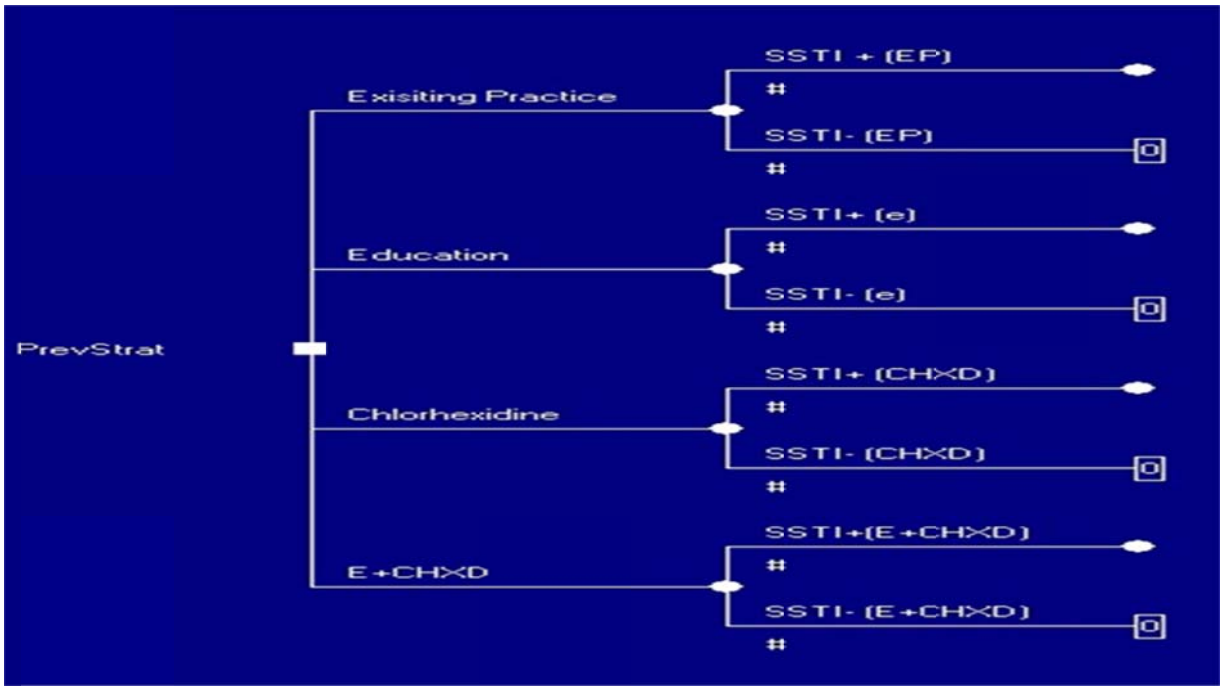


Figure 8 Prevention strategies model

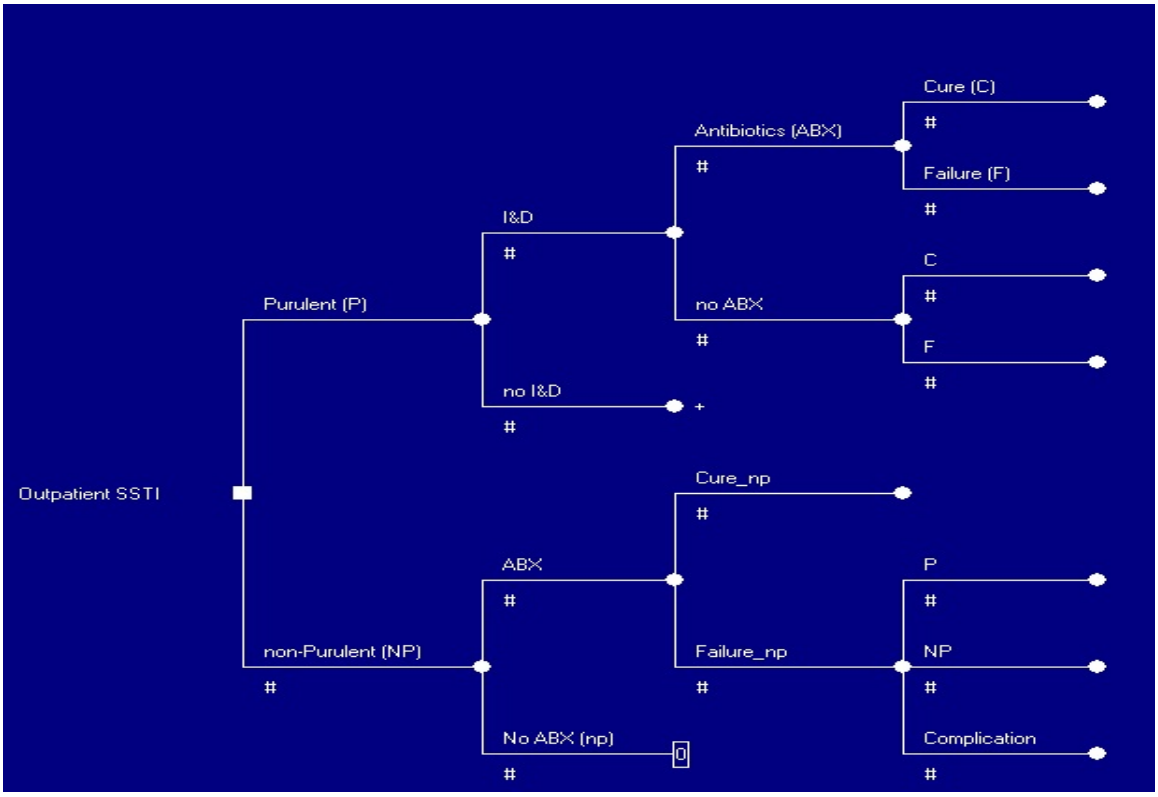


Figure 9 Existing practice model

Model assumptions

Assumptions will be made when creating the conceptual models. Information regarding infection (MRSA prevalence), effectiveness estimates (QALYs), and other factors such as parameter distribution (e.g. cost data are skewed and can take the form of a gamma distribution) may influence the model. In building the models, these assumptions will be outlined and considered in subsequent sensitivity analyses.

Data collection

Cost, effect, and health status data will be derived from a combination of primary and secondary data sources (i.e. FB MRSA study and data obtained from objectives 1-3).

The FB MRSA study, as previously described, will provide data collected over a 20-month period. Patient-level information including demographic, risk factor, hospitalization, and microbiologic variables will be captured in this dataset. Primary endpoint information, rates of SSTI will also be obtained from the FB MRSA dataset. Cost information, can also be obtained using costs estimates obtained from the MDR. These data will be used to provide estimates for the "real-world" model constructed above.

Additionally, secondary, existing data will also be used for this CEA. These data will provide estimates for the "evidence-based" model as well as provide a baseline for the "existing practice" models constructed above. All relevant health, cost, and effect variables are listed in the tables in **appendix K**.

Cost-effectiveness computation

Cost evaluation

Costs estimates regarding clinical and hospital care as well as lost time in training will be derived from objective 2's cost of illness model and data obtained from the FT Benning MRSA study. Time horizons and discount rates were described earlier in this section. When possible, actual costs as opposed to charges will be used to obtain a more conservative estimate of fiscal burden. Cost-to-charge ratios will be applied to adjust hospital charges to better estimate costs actually used when a patient is hospitalized. Muening et al. provides simple calculation using information related to the DRG and Medicare charges to calculate the opportunity cost for a charge.(149) This estimate reflects the actual societal resources used to pay for a hospitalization. It can be used if only charge data are available.

Evaluation of effectiveness

Effectiveness estimates will be obtained through the FB MRSA study as well as objective 3's systematic review of the literature. Point estimates (odds ratio, relative risk, and prevalence) will be calculated along with 95% confidence intervals. Quality Adjusted Life Years (QALYs) will also be calculated based on the published literature.(119; 206) According to the US Panel on Cost-Effectiveness in Health and Medicine (168; 206), the QALY allows for comparability in CEA across different health-care interventions. Because the QALY is not always easily understood effects will be measured with regards to disease as well as QALYs in the incremental cost effectiveness ratio. Both approaches to the effectiveness estimate have been used in previous CEA studies.(30; 36; 119)

Calculation of the average cost-effectiveness ratio (Average CER)

Average CER will be calculated for each of the strategies in each of the models outlined. General calculations are provided below. These calculations were derived from Gold, Brown and Bothavong.(30; 36; 77) Costs estimates will be generated from objective 2 and the FB MRSA study. Effectiveness estimates will be obtained from objective 3 and the FB MRSA study. All cost effectiveness calculations and outcomes can be found in **appendix K**.

Calculation of the Incremental Cost-effectiveness ratio (ICER)

ICER will be calculated for each of the strategies in each of the models outlined above. Appendix K includes generic calculations provided by Gold, Brown, and Bounthavong.(30; 36; 77) This ratio is generated to assess the additional cost per infection avoided compared to the next effective strategy.(77) Costs estimates will be generated from objective 2 and the FB MRSA study. Effectiveness estimates will be obtained from objective 3 and the FB MRSA study.

Ultimately, upon inspection of the incremental cost-effectiveness ratio, an assessment will be made as to which strategy is the dominant strategy. A dominant strategy is defined as being less costly with increased effectiveness over the other strategies.

Assessment of uncertainty in CEA

Probabilistic sensitivity analyses will be performed to test the effect of varying key parameters that have a large degree of uncertainty surrounding them. These include parameters in which multiple assumptions were made to generate an estimate. One-way and multi-way sensitivity analyses will be done to examine the absolute impact on the incremental cost and effects of changes among selected parameters with all other

parameters held constant. Parameters in this sensitivity analysis include: prevalence of MRSA (1-5%), prevention program compliance (1-5%), duration of prevention program (3 months to 1 year), cost distribution type (beta vs. gamma), discount rate (2-4%), and intra-correlation coefficients for cluster-randomized data (0.001-0.10), and imputation uncertainty for missing data. Monte Carlo simulations will be used to simultaneously vary the values of each parameter and generate a confidence interval for the ICER. Variables included in the sensitivity analyses will be obtained from data collected in the FB MRSA study and objectives 1-3.

DATA PROTECTIONS AND DATA USE AGREEMENTS (DUA)

The principal investigator will work in collaboration with personnel from the Infectious Disease Clinical Research Program (IDCRP), Army Public Health Command-Provisional (APHC), and the Navy Marine Corps Public Health Center (NMCPHC) to acquire Data Use Agreements (DUA) for de-identified datasets and obtain data necessary for the study. USAPHC and USUHS researchers are HIPAA certified and compliant.

MHS Mart (M2) and Defense Manpower Data Center (DMDC) datasets ranging from 2006 through 2009 will be provided by the US Army Public Command's (USAPHC-provisional) Directorate for Epidemiology and Disease Surveillance, Disease Epidemiology Program researcher. Individual level M2 data will be provided to the principal USUHS investigator. Demographic, disease, and cost variables will be included in the dataset. DMDC data will provide person-time information. The USAPHC (Prov) researcher will make the link between M2 and DMDC datasets. The data will be de-identified and password protected prior to furnishing the USUHS principal investigator. USAPHC (Prov) currently has DUAs in place with both TRICARE and DMDC.

Requests for DMDC data will be made using a Specific Projects Attachment form. Each SPA will list the variable identifiers that USAPHC (Prov) requests from the specific data source (e.g. CTS, DEERS) and will provide a justification for the request that the variable be included in the extract. Additionally, USAPHC (Prov) has DUAs established with NMCPHC to receive feeds of HL-7 data. Personnel from USAPHC (Prov) will work with NMCPHC to link Health Level 7 microbiological data with M2 and DMDC datasets in order to provide the principal investigator with a completely de-identified dataset.

The USAPHC researcher will also provide population summary data (also password protected) from DEERS from 2006-2010. The populations data are aggregated and do not contain personal identifiers. They will also be used to generate summary statistics and rate determination.

Research data obtained from IDCRP-055- Fort Benning MRSA Study Protocol will not include Identifiable Protected Health information. A restricted dataset will be provided to the PI for analysis. Data will be maintained under the standard operating procedures for data management established at the IDCRP.

SUMMARY AND PUBLIC HEALTH SIGNIFICANCE

The on-going CA-MRSA epidemic has been well documented and treatment of community acquired infections can be challenging. SSTIs attributed to *S. aureus* are prevalent in the community and the literature has demonstrated the burden of such infections in the health system. Infections have contributed to an increased number of ambulatory visits to outpatient facilities and emergency departments. Additionally, lack of knowledge about SSTI and the appropriate clinical care procedures can lead to unnecessary antimicrobial therapy. Young, healthy, military populations are increasingly

at risk for infection which can lead to lost time in training or severe infection requiring hospitalization.

Many hygiene-based prevention strategies have been recommended by the CDC, BOP, and also military institutions such as NEHC. Such strategies usually ensue subsequent an outbreak. Although these measures have been issued and instituted for a number of years within congregate settings, little is known about their effect in preventing community acquired SSTI and possibly infections that follow the same transmission pathway. This study will determine costs associated with such programs in high incidence settings which can then assist in implementing the most cost-effective measures in the active duty military population. Perhaps, prevention strategies found cost-effective could be instituted in similar settings such as in prisons or sports facilities. Even if the strategies are effective at preventing infection, if they are not cost-effective, policymakers might not be willing to implement such prevention measures on a grand scale. The series of cost estimates generated from this evaluation can provide further insight into the magnitude of the problem. If results show a significant impact on burden and costs of disease, could prove to be useful in other similar congregate populations (i.e. inmates, athletes).

Organisms resistant to antibiotics are endemic in community settings as well as emerging. The most efficient and cost beneficial prevention strategies need to be discovered and adopted to wean the public of their reliance on antimicrobial agents to treat infections. If use of antibiotics is necessary, understanding the disease burden and being educated as to standard clinical care procedures in the community can prove

beneficial in choosing appropriate therapies. Simple and cost-effective prevention measures are necessary to tackle SSTI and MRSA-SSTI in the community.

Chapter 2 Systematic review and meta-analysis of hygiene strategies for prevention of directly transmissible communicable illness like *S.aureus* skin and soft tissue infections

BACKGROUND

A need exists for a thorough evaluation of the literature to determine effective primary prevention measures aimed toward skin and soft tissue infections with *Staphylococcus aureus* (*S.aureus)* involvement. Recommended measures from federal to community level organizations include a focus on personal hygiene, education, and use of soap and water while washing hands (**appendix B**). An evidenced based review is required to determine the effectiveness of these measures individually and combined against *S.aureus* SSTI.

Little literature is available, specifically in the high-risk community setting that has studied efforts to reduce infections, costs, or days of lost productivity when such infections occur. One study that explored personal hygiene efforts against methicillin resistant *Staphylococcus aureus* (MRSA) attempted to evaluate cost-effectiveness.(172) Although multiple studies could be found with an emphasis on hand washing and hand hygiene education directed toward the daycare and elementary school populations but less was available with respect to the military. Studies including assessment of lost-productivity were found for studies with RI and GI disease outcomes in the community setting but not for SSTI or MRSA. (85; 148) Most studies conducted are either in hospital settings or directed at hospital populations with respect to skin infections caused by MRSA. Additionally, most studies published recently within the community setting focus on primary prevention toward illness with gastrointestinal or respiratory involvement.

A brief assessment of the literature yielded 5 Cochrane Reviews (**table 1**). Two reviews assessed the impact of non-pharmaceutical measures on diarrhea and respiratory viruses among adults and children, one review evaluated the effectiveness of antiseptic

pre-operative bath and shower on surgical site infections, and two reviews sought to determine the effect of antibiotics on skin infections such as cellulitis and impetigo. With respect to skin infections, no known systematic review with meta-analysis exists in the literature to evaluate primary prevention measures (i.e. showering with chlorhexidine) in the community setting. Additionally, other systematic reviews have evaluated hand hygiene to prevent gastrointestinal and respiratory illness, but no one review specifically assessed personal hygiene measure (5; 90; 135) to include showering and use of chlorhexidine in a high-risk community population setting with emphasis on prevention of SSTI or MRSA-SSTI. One systematic review without meta-analysis reviewed risk factors for CA-MRSA among inmates and military but did not evaluate the effects of any programs on these risk factors.(5)

Considering poor hygiene is a major contributor to increased skin and soft tissue infections caused by *S.aureus*, little is understood about hygiene programs' effects on rates of overall, *S.aureus* and MRSA SSTI. Specifically, less is known about individual components of a prevention program to include methods such as use of chlorhexidine body wash, hand hygiene (soap or hand sanitizer), hygiene education (disease transmission and techniques by which to interrupt transmission, and disinfection as well as used in concert. Many organizations recommend using these measures for outbreak and infection control in semi-enclosed settings, but a strong evidence based study should be done to determine whether these measures are effective in reducing rates, risks, and absences.

The objective of this systematic review is multi-fold. First, to identify studies in the community populations using prevention measures described above to reduce rates of

directly transmitted acute communicable disease (i.e. hand to hand transmission) and days absent from these diseases. The overall hypothesis is using multiple hygiene based measures either individually or combined could prevent or reduce rates of directly transmissible acute communicable illness like *Staphylococcus aureus* skin and soft-tissue infection (herein called *S.aureus* SSTI).

Description of study outcomes

Primary outcomes include rates of communicable illness-specifically, gastrointestinal, respiratory, and skin related illnesses (CI, GI, RI, and SI, respectively). Secondary outcomes include costs of preventive programs and absenteeism rates and days lost from infectious illness.

Description of interventions

Interventions of interest are based on the recommendations provided by multiple organizations for the primary prevention of acute CI. These interventions include hand hygiene, personal hygiene, hygiene education, disinfection, or a combination of these interventions. Hand hygiene evaluates a product and a method of application to include hand washing or sanitizing with soap or an antibacterial agent. Personal hygiene evaluates a product such as chlorhexidine and a method of application like showering. Hygiene education only educates, no product (i.e. soap or chlorhexidine) is provided; it includes information regarding direct disease transmission prevention, measures of an education program (posters, lecture sessions, booklets, etc.), and hygiene techniques (how to apply soap/ wash hands/ shower).

Study design and population

Study design types that were observational-analytic or experimental in nature were considered for inclusion into this systematic review. Case series or case reports were excluded. Additionally, the study population included those within high risk community settings for directly transmissible acute CI. These settings included households, schools, daycare, military training facilities, jails, and outpatient clinics. With respect to outpatients, the population did not include those study participants who were hospitalized, in long-term care facilities, had co-morbid conditions, or immunocompromised.

SEARCH STRATEGY

Resource constraints allowed for only one searcher. Searcher is a doctoral student with knowledge of systematic reviews. Searcher consulted professors, university librarians, and peer-reviewed literature prior to start of the search to identify and create a search strategy that would yield reasonable results.

A detailed search strategy can be found in **appendix L**. The search covered the time period from 1980 through 2014. Keywords were grouped by category to include intervention, outcome, method of application, and study design. Only two variables changed during each search- outcome and intervention- method of application and study design remained constant. Additionally, studies were limited to English language and human subjects. No contact was made with any of the authors as this was not deemed necessary.

Four databases were searched to include Medline, Excerpta Medica database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and

the Cochrane review. MeSH terms were used with explosion within PubMed/Medline. Additionally hand searching was performed using systematic review articles.(5; 90; 102; 135) No abstracts were included in this study and reviewer (SMM) retrieved all published articles. No contact was made with any of the authors.

Approximately 9,800 citations were retrieved in the final keyword search (**Figure 10**). Furthermore, 672 citations were retrieved for further abstract review. Detailed assessment of the article was performed on 126 citations-this assessment included evaluation of the entire publication. Data extraction and quality assessment was performed on 64 of these citations. The other 62 citations were excluded for the following reasons population, outcome or intervention outside of study scope (n=25); lack of data to recalculate rates (n=12); review article (n=14), and language other than English (n=1). Overall, 42 citations were included in the meta-analysis. A complete list of citations located and those excluded (along with justification) can be found in **appendix M and N**.

One of the limitations included in the search filters was English only; therefore, articles in languages other than English were not searched for but one was identified because the abstract was in English. Searcher attempted to evaluate and abstract information from article but found it did not meet inclusion criteria.

METHODS

All study types except for case-series and case reports were considered for this study. With respect to overall, S.aureus, and MRSA SSTI-most information available is non-Randomized Controlled Trials (RCT) or observational analytic studies; therefore, many of these would have been excluded from the review if not considered. This could

be a source of confounding and heterogeneity and is analyzed further in the meta-analysis. Designs were categorized into experimental, observation-analytic, and cost-effectiveness analysis. The experimental group included RCT, non-RCT and quasi-experimental. The observation-analytic group included prospective and retrospective cohorts as well as case-control and ecologic studies.

Studies were included if they had an intervention, population, and outcome of interest; furthermore, the study needed to include enough data in which rates, days, rate ratios, 95% CI, and p-values could be recalculated. Primary elements necessary required for the calculation of rates included the number of outcomes, the total population in each group, and the duration of the study. The rate was re-calculated for each study so that the rates were all standardized to the same scale (odds ration vs risk ratio) and unadjusted (rates reported that adjusted for confounding variables). A total of 64 citations were retrieved for data extraction and quality assessment (**figure 10**). Only 42 of these studies were assessed further in the meta-analysis, the other 22 were excluded because of an inability to re-calculate effect estimates with the data available (absolute numbers of outcomes and total population were missing) and one study was included that was a duplicate of another study reported in different years.

Data selection was based on previous literature reviews with similar interests.(5; 135) The data extraction tool was modified based on the purposes of this study. Ultimately, this study sought to calculate a pooled estimate of effect that would be used in further analysis. Data were categorized based on study characteristics, study design, population and setting, type of intervention, type of outcomes (primary and secondary) as well as effect estimates. For the effect estimates to be re-calculated for each intervention

absolute numbers of cases or episodes were collected for each group as well as the total population for each group. The risk ratio was calculated for each arm of the study as well as by outcome combined and individually. Data with multiple rates were categorized by outcome and reported separately. Additionally, if the data had multiple exposures (or study arms) the rates were reported for each arm of the study. Potential sources of confounding include study design type, study setting and population, and quality of the study. Data were collected on these variables in order to evaluate their effect on the risk estimates in sensitivity analysis.

Two reviewers assessed the quality of the studies (SMM and CS). A quality assessment tool by Downs and Black included 27 questions and evaluated five factors related to reporting, external and internal validity (bias and confounding) as well as power.(60) The two reviewers assessed a 10% sample of the 64 included studies to assess scoring agreement between the reviewers. Results of the 10% sample showed that the reviewers agreed on most questions. Any conflicts were resolved after the reviewers discussed the questions and came to a consensus regarding how to score the question. The disagreement occurred with respect to one question concerning bias and one question concerning confounding.

To assess heterogeneity, the following statistics were used. These methods have been used in previous, similar reviews.(5) To determine the existence of heterogeneity and the amount of variation in the risk ratio attributable to heterogeneity, the I^2 statistic was used.(27) The Q statistic was used to assess between study variability with a random effects estimate.(27; 181) Sources of heterogeneity were explored using meta-regression.(27; 88; 94; 192) Additionally, funnel plots with Egger's test were used to

observe potential publication bias. All meta-analyses were performed using STATA software and corresponding STATA commands (METAN, META, METAREG, and METAFUNNEL).(32; 88; 94; 181; 188) METAN produced pooled effect estimates along with tests for heterogeneity and I^2. Heterogeneity was deemed significant at $p<0.05$. I^2 is used to determine the proportion of the pooled estimate attributable to heterogeneity. Additionally, this command derived forest plots to visually inspect results and the amount of weight each study contributes to the estimate. The estimate of effect was the risk ratio. The META command generated the fixed and random effects pooled estimate along with the Q-statistic for between study variability as well as a forest plot to visually inspect this variability. METAREG allowed searcher to assess potential sources of heterogeneity around the pooled estimate (p-values<0.05 considered significant). Last funnel plots and Egger's tests were produced by the METAFUNNEL command to evaluate publication bias.

RESULTS

Data were extracted and study quality was assessed for 64 citations. Most of the included studies were conducted between 2000 and 2009. Three-quarters of the studies were implemented in developed regions and about one-third were performed in the elementary school population. Randomization occurred in about half of the studies. Most of the studies evaluated the impact of hygiene strategies on respiratory illness. Hand hygiene and hand hygiene promotion were the most prominent interventions. (**Table 2**)

With respect to skin infections, personal hygiene along with an educational component occurred most often. Personal hygiene commonly included a shower with an antibacterial agent like chlorhexidine (beyond hand washing alone), limiting the sharing

of personal items, and reporting of infection by a third party. Additionally, use of these measures was most often observed among inmates, military members, or persons from outpatient facilities.

Quality assessment

Most of the included studies in the meta-analysis (n=42) were rated as either moderate (n=23) or good quality (n=16). The mean quality assessment score was 19.2±4.65 standard deviations (range: 8-27) (median=20 IQR=6.25). Most of the good studies (82%) were RCTs. All non-RCTs were deemed to be of moderate quality and most analytic observational studies (i.e., prospective cohorts, case-control) (85%). Only 3 studies were rated as poor-two of which were outbreak investigations and one quasi-experimental study. Sensitivity analysis was performed to evaluate differences between studies scored as good compared with those scored as moderate or poor. Results showed that studies of moderate quality inadequately reported confounding, losses to follow-up, the source population, statistical methods used, compliance, allocation concealment, adjustment for confounding and losses to follow-up. Poor studies were inadequate in multiple areas of reporting, external and internal validity as well as power of the study compared to studies with a good quality assessment score.

Combined illness

Forest plots and Mantel-Haenzel pooled estimates were derived for disease combined and then separately for RI, GI, and SI (**Tables 3-7** and **Figures 11-14**). For illnesses combined, the pooled risk ratio (RR) showed a slightly beneficial effect of the interventions combined (RR=0.87; 95%CI: 0.85, 0.91). Range of risk ratios include a low of 0.44 (multifactorial intervention) to a high of 1.36 (hygiene education + personal

protective measures). (**Table 3**) Removal of studies with wide CI's and outlying weights moved the pooled estimate slightly, but did not improve heterogeneity which remained significant (RR=0.87; 95%CI: 0.84, 0.90; chi-square=229.71, d.f. =50, p<0.0001; I^2=78.2%). Significant variability existed between studies (Q=229.51, d.f.=50, p<0.0001). Potential sources of heterogeneity were explored. Variables included study design, study setting, study population, study year, quality assessment scores, infection type, and intervention type. Significant sources of heterogeneity around the pooled estimate were not found when all infections and interventions were combined. Although not significant, year of study explained about 10% of the between study variance p=0.085.

Gastrointestinal illness

Individual effect estimates ranged from a low of 0.29 (infection control bundle) to a high of 1.03 (Hand Hygiene Promotion) (**Tables 3, 5**). On average, risk ratios showed a beneficial effect of the interventions combined [0.70 (95% CI: 0.51, 0.98]. Pooled estimate assessment-initial pooled estimate showed a beneficial effect of all interventions combined with a pooled risk ratio of [0.75 (95% CI: 0.71, 0.79)], but significant heterogeneity was found (chi-square=45.68 (DF=18) p<0.0001, I^2=60.6%). Inspection of the forest plot identified three studies that were possible contributors to heterogeneity (**Figure 12**). Removal of the studies barely attenuated the protective effect (RR=0.77; 95% CI: 0.72, 0.81), reduced the chi-square estimate (32.57, d.f.=15), increased the p-value (0.005), and I^2 also reduced to 53.9%. Additionally, heterogeneity existed between studies (Q-statistic =32.55, d.f. =15, p=0.005)**.** Potential sources of heterogeneity include the design type and the quality assessment score. As the quality of the study improves, the effect estimate moves towards the null.

Respiratory illness

The pooled risk ratio was 0.77 (95%CI: 0.75, 0.80) (**Tables 4, 6**). Significant heterogeneity was found (chi-share=224.29 (d.f.=22) p<0.0001 I^2=90.2%). (**Figure 13**) Variability between studies was also found (Q=222.17 d.f=22, p<0.0001). The pooled estimate sided toward beneficial for both fixed and random effect models, but the fixed effects model showed a slightly higher protective effect compared with the random effects estimate. Potential sources of heterogeneity were explored. Intervention type was significantly associated with heterogeneity (p=0.022). Upon inspection, risk of respiratory illness seems to improve with a mixture of hand hygiene and education as opposed to just hand hygiene alone. (**Table 6**)

Skin infection outcomes

Most of the studies were conducted in semi-enclosed settings; although, one study by Luby *et al*, evaluated soap and antibacterial soap on the rate of impetigo among children. (123) The mean risk ratio was 1.83 ±2.87 while the median leaned toward a protective effect at 0.78 (IQR=0.80). Risk ratios ranged from 0.04-12.6 across the included studies. (**Table 7**) The Mantel-Haenzel pooled estimate was 0.92 (95%CI: 0.90, 0.94). (**Table 3**) Test for heterogeneity was significant (chi-square=342.85, d.f. =22, p<0.0001). The I^2 indicated that 93.6% of the variation in the risk ratio was attributed to heterogeneity. (**Figure 14**) Sensitivity analysis was performed to evaluate the effect of removing studies with extreme weights in either direction on the risk estimate. Results showed that upon removal of five studies, heterogeneity still remained, but the effect estimate moved toward increased beneficial effects with a pooled RR of 0.79 (95%CI:

0.70,0.89) chi-square=33.54, d.f.=10, p<0.0001. The I^2 improved as well (70.2%). Significant between study variability was observed (Q=33.2, d.f.=10, p<0.0001). Differences were also observed between the fixed and random effect estimates. Both estimates were deemed beneficial, but the random effect estimate was not significant as opposed to the fixed effects estimate. Potential sources of heterogeneity were explored to include the study design, the intervention type, whether the intervention was in response to an outbreak, the population type, the study setting, and quality assessment scores. Significant associations were not found among these variables and heterogeneity around the effect estimate.

Pooled estimates should be considered with caution. Weights of some good studies are so low that they did not contribute much to the estimate. Sensitivity analysis revealed that removal of certain studies influenced the estimate of effect and the variation found between studies. Sources of heterogeneity need to be explored further. Although not significant, quality scores with respect to external validity and outbreak response accounted for 11.8% and 19.1% of the variation between studies respectively.

Publication bias was explored among all studies and all disease outcomes and disease outcomes separately. Egger's test and funnel plots were used to observe any potential publication bias. Additionally, publication bias was explored by study design type and quality assessment score. Publication bias was not found.

DISCUSSION

Guidelines for prevention of communicable illness

Multiple organizations have developed specific guidelines for the primary prevention of directly transmissible communicable illness like *S.aureus* SSTI within community populations. Guidelines often include an educational component, a hand hygiene program, sanitation and personal hygiene recommendations. No one study evaluated each of these practices separately and then in combination. These guidelines are thought of as best practices but little is known about the effect of each recommended component and in combination. Often guidelines implemented as a bundle. Multiple studies have evaluated the impact of hand hygiene and hand hygiene programs on rates of respiratory and gastrointestinal illness, but little is available with respect to skin infection. The guidelines for prevention of skin infection often include enhanced surveillance like inspection of wound infections and personal hygiene components as well as decolonization of skin. Little is known about the effectiveness of these factors on the rates of skin infection. Through this systematic review findings revealed that there is great variation between studies with respect to outcome and intervention.

Infection control measures evaluated in response to an outbreak for skin illness

Studies assessing the impact of an intervention on skin infection outcomes were a mix between controlled trials within an outpatient setting and response to an outbreak. Primary prevention measures were not often evaluated in the military and jail setting; conversely, secondary prevention was more often evaluated such as containment, infection control measures, and surveillance. Additionally, the use of chlorhexidine has been recommended in each of these settings for skin and soft tissue infections, but was

not found to be used for gastrointestinal or respiratory infections. Often basic hand washing with soap and water or with an antibacterial agent was evaluated for impact on GI and RI. Only one study evaluated the impact of hand washing with soap or antibacterial soap on impetigo among children. This study yielded mixed results. Use of soap had a beneficial effect while use of antibacterial soap increased risk of impetigo among children.(123) Studies that were not in response to an outbreak usually yielded results that were directed toward the null or increased risk while studies of outbreak response usually showed extremely beneficial results.

Assessment of bias

Considering observational –analytic studies, non-randomized and randomized controlled trials were included in the meta-analysis, observation and selection bias likely exist-the extent to which is unknown. Study weights were extreme for observational-analytic studies. In sensitivity analysis, these studies were removed and did not improve the between study variance or the variance around the risk ratio. Each study included in the meta-analysis was assessed for quality. Most studies were either of moderate or good quality. This could be attributed to the fact that studies of poor quality were excluded before the quality assessment occurred. The quality assessment was only performed on included studies; therefore, bias could be a contributor here. Publication bias was not found with the use of Egger's test or funnel plots.

The studies were of mixed quality. Studies on hygiene strategies aimed toward skin infection were usually retrospective without randomization. Conversely, most studies evaluating non-pharmacologic methods aimed toward primary prevention of RI and GI were at least experimental in design and many were randomized trials.

CONCLUSIONS

Overall, this study showed that primary prevention measures such as hand hygiene and hand hygiene promotion can be effective in reducing risk of common acute gastrointestinal, respiratory and skin infections. Pooled estimates ranged from a low of 0.74 to a high of 0.92. Caution should be heeded as significant heterogeneity surrounded the effect estimates. The variation around the estimates could be explained by the study weights. Studies with larger samples and more cases influenced the pooled estimate. The weights were not equal among the studies. Studies in which one would consider to be of quality design did not add as much weight to the estimate as did the studies that were observational-analytical. Smaller weights, lead to wider confidence intervals around the effect estimate and greater weights contribute to tighter confidence intervals around the effect estimates. Sensitivity analysis showed that removal of studies with attenuated or exaggerated weights influenced the pooled estimate but did not have a significant effect on the heterogeneity observed. Contributors to these weight differences likely exist beyond study design, but more information needs to be collected to identify these specific factors.

During data extraction, information was collected on study design (year, type, population, setting) and study quality (reporting, validity, and power) in hopes to evaluate potential sources of heterogeneity. Results showed that for GI design type and quality score were associated with heterogeneity; while for RI only intervention type was significantly associated with heterogeneity. Interestingly enough, although heterogeneity around the pooled estimate existed for CI and SI, the sources could not be explained. Other sources of heterogeneity could not be explored. For instance, with respect to SI, seasonality could be influential on the risk ratio. Depending on the time of the year the

study was conducted one could see a beneficial result while another study could show increased risk.

Most interventions involving hand hygiene and hand hygiene promotion were implemented among school children and households. Conversely, those interventions involving personal hygiene promotion and chlorhexidine use usually occurred among athletic teams, military personnel, and inmates. Although not found to be a significant source of heterogeneity, the differences in populations does influence the effect estimate toward the null. The studies conducted among households, daycares or elementary schools showed a beneficial pooled estimate (RR=0.85; 95%CI: 0.79, 0.85) while the studies conducted among military, inmates and athletes showed non-significant benefits (RR=0.95; 95%CI: 0.90, 1.02). Studies conducted in the school setting are often randomized while in settings like the military-the study is in response to an outbreak and often deemed public health surveillance. Generalizing the results from this review should only be done to specific, targeted populations, and even then should be done so with caution.

Much of the work that has been done in the area of primary prevention of communicable illness has been limited to evaluating the impact of such programs on the rates or risk of infection. Little has been done in the area of cost-effectiveness analysis. Although some of the programs seem to generate beneficial effects, scarce documentation exists regarding the cost of these programs and their overall cost-effectiveness. Many of the studies in this review cited costs as being a limitation in sustaining many of these prevention programs. The cost of resources-both medical and non-medical, tangible and intangible have not been fully explored. This review obtained one actual cost-

effectiveness analysis that used modeling techniques to generate cost-effectiveness ratios. (43) Two other studies (85; 172) attempted to estimate costs and costs savings of the program implemented. Two studies evaluated effects of the intervention on lost-time from work.(148; 174) Results from this review can be used in conjunction with information obtained from a prospective analysis to perform cost-effectiveness analysis and determine which hygiene component is not only beneficial but is not expensive to implement.

The primary objective of this systematic review and meta-analysis was to derive effect estimates for primary prevention efforts towards acute communicable illness such as skin infections with *S.aureus* involvement. Prevention methods such as hand and personal hygiene, education, and disinfection have been recommended by multiple organizations to prevent and reduce the spread of disease in community populations. This review hoped to observe an impact of each individual technique as well as all methods used in conjunction with one another on the risk of communicable disease. Because of the significant heterogeneity surrounding the effect estimates, it is difficult to discern which estimates would apply for use as baseline estimates in a cost-effectiveness analysis.

In making the selection of estimates for future use in cost-effectiveness analysis, three factors were considered-the population of interest, study design, and the way in which the intervention was implemented. The target population for the cost-effectiveness analysis is the community, but the specific population of interest needs to be examined further. Including those study estimates derived from an outpatient or household population might not be as applicable as those estimates from semi-enclosed settings such

as a military facility or jail. Secondly, the way in which the intervention was implemented needs to be considered as well. As was noted previously, studies of interventions within the military or inmate population were often in response to an outbreak rather than being design a priori. Last, the study design has an influence on the effect estimate. Studies that were observational-analytic in design showed pooled risk ratios with increased benefit when compared with randomized controlled trials (0.72 and 0.85, respectively). In the cost-effectiveness analysis, using an effect size that overestimates the benefit could substantially influence cost-effectiveness ratio and therefore should be used with caution.

This is the first known review and meta-analysis that aimed to evaluate the impact of hygiene strategies on communicable illness, specifically with the inclusion of skin infections. Ultimately, this review set out to generate effect estimates of recommended techniques to prevent and reduce the spread of acute communicable illnesses. Pooled results showed that such methods can be beneficial, both separately and in conjunction. Although, significant heterogeneity surrounded the pooled estimates, this is a good addition to the evidence base regarding recommendations for the prevention of communicable illness and the ability to sustain such efforts in a cost-effective manner.

Table 1 Cochrane reviews for hygiene measures impact on acute communicable illness

Study	**Year**	**Outcome**	**Intervention**	**Population**	**1°, 2°,3° prevention**
Ejemot (63)	2009	Diarrhea	Hand washing	Community	Primary
Jefferson (102)	2010	Respiratory Virus	Hand washing Disinfection PPM (masks & gowns)	Adults & Children	Primary
Kilburn (107)	2010	Cellulitis & Erysipelas	Antibiotics	Adults & children	Tertiary
Koning (110)	2012	Impetigo	Antibiotics	Adults& children	Tertiary
Webster (205)	2012	Surgical site infection	Pre-operative bathing & showering (chlorhexidine)	All surgical patients	Primary

Table 2 Characteristics of Included Studies

Study years	n	%
1980-1989	2	3.0
1990-1999	14	21.2
2000-2009	32	48.5
2010-2014	18	27.3
Country		
Developed	50	75.8
Less developed	16	24.2
Setting		
Elementary school	21	31.8
Household/neighborhood	16	24.2
Daycare	10	15.2
Military facility	7	10.6
Jail	3	4.5
University	2	3.0
Outpatient clinic	2	3.0
Athletic team	1	1.5
Other	4	6.1
Randomization		
Yes	32	48.5
No	34	51.5
Infection outcomes/symptoms evaluated[1]		
GI	**30**	
Diarrhea	36/103	35.0
Vomiting	15/103	14.6
RI	**45**	
Cough	35/103	31.8
Fever	32/103	27.3
Sore throat	15/103	22.7
SI	**20**	22.3
MRSA	14/103	13.6
Intervention[2]		
Chlorhexidine wipes	3/64	4.7
Hand hygiene (soap, hand sanitizer)	22/64	34.4
Hand hygiene promotion (soap or hand sanitizer + education)	21/64	32.8
Personal hygiene promotion (chlorhexidine + education)	6/64	9.4
Hygiene education only	5/64	7.8
Disinfection	2/64	3.1
Multifactorial (disinfection + hygiene promotion)	4/64	6.3

[1]Multiple studies reported on more than one disease outcome. [2]Multiple studies reported more than one intervention arm.

Table 3 Interventions and outcomes, Mantel Haenzel pooled risk ratios (95%CI), test for heterogeneity, and I^2

	All Interventions	**Hand hygiene (HH-Soap, ABS, ABHS)**	**Personal hygiene (PH-Chlorhexidine)**	**Hygiene Education (HE)[2]**	**HH+HE**	**PH+HE**	**Disinfection[2]**
CI	0.79 (0.77,0.80) p<0.0001 I^2=87.9%	0.83 (0.79,0.86) p<0.0001 I^2=75.0%	0.90 (0.71,1.14) p<0.0001 I^2=63.5%	0.78 (0.62,0.99) p=0.041 I^2=63.5%	0.77 (0.75,0.79) p<0.0001 I^2=89.2%	0.69 (0.65,0.72) p<0.0001 I^2=91.7%	0.61 (0.34,0.1.10)
GI	0.77 (0.73,0.81) p<0.0001 I^2=88.3%	0.768 (0.72,0.83) p=0.0001 I^2=78.5%		0.94 (0.62,1.42)	0.79 (0.77,0.80) p<0.0001 I^2=87.9%		
RI	0.76 (0.74,0.79) p<0.0001 I^2=88.3%	0.88 (0.83,0.94) p=0.004 I^2=64.6%		0.72 (0.54,0.97)	0.74 (0.72,0.77) p<0.0001 I^2=91.6%		0.61 (0.34,0.1.10)
SI	0.83 (0.80,0.87) p<0.0001 I^2=92.1%	0.85 (0.72,1.01) p<0.003 I^2=82.5%	0.90 (0.71,1.14) p<0.041 I^2=63.5%		0.98 (0.91,1.05) p<0.058 I^2=72.2%	0.68(0.65,0.72) p<0.0001 I^2=91.9%	

[1]Each cell includes the pooled M-H risk ratio with 95% CI, test for heterogeneity p-value, and the I^2 which indicates the proportion of the relative risk attributable to heterogeneity.
[2]Only one study included for specific outcome; therefore, tests for heterogeneity and I^2 could not be calculated.

Table 4 Unadjusted risk ratios of acute CI using hygiene prevention strategies

Study	Year	Outcome	IG1	IG2	RR (IG1vsCG)	LCI	UCI	RR (IG2vsCG)	LCI	UCI
Black[26]	1981	GI	HH		0.66	0.47	0.91			
Han[22]	1989	GI	HH		0.77	0.63	0.96			
Shahid[179]	1996	GI	HH		0.62	0.55	0.71			
Falsey[68]	1999	RI	HH		1.2	0.72	2.03			
Falsey[68]	1999	RI	HH		0.93	0.6	1.44			
Luby[†123]	2002	SI	HH (S)	HH (ABS)	0.65	0.5	0.85	1.13	0.91	1.41
Boulware(29)	2004	GI	HH		0.55	0.29	1.07			
Larson(117)	2004	GI	HH		1.01	0.72	1.41			
Larson[117]	2004	RI	HH		0.89	0.81	0.98			
Larson[117]	2004	SI	HH		0.52	0.21	1.29			
Luby(125)	2004	GI	HH	Other	0.87	0.7	1.09	0.66	0.5	0.88
Luby(125)	2004	GI	HH	Other	0.69	0.56	0.85	0.35	0.24	0.5
Morton[147]	2004	RI	HH		0.62	0.44	0.89			
Van Camp[197]	2007	RI	HH		1.09	0.07	16.99			
Larson(116)	2010	URI	HH	Other	0.87	0.67	1.13	0.75	0.56	0.99
Larson[116]	2010	ILI	HH	Other	1.15	0.67	1.96	1	0.58	1.74
Prazuck[161]	2010	GI	HH		0.67	0.51	0.89			
Savolainen[174]	2012	GI	HH	HH	0.87	0.75	1.01	1.08	0.94	1.24
Castilla[39]	2013	RI	HH (ABHS)		1.19	1.01	1.39			
Whitman[213]	2010	SI	CHX		1.25	0.86	1.84			
Fritz[75]	2012	SI	CHX		0.78	0.55	1.1			
Fritz[75]	2012	SI	CHX		0.35	0.14	0.83			
Miller[142]	2012	SI	CHX		0.97	0.4	2.36			
Mahooney[126]	1991	GI	HE		0.94	0.62	1.42			

Study	Year	Outcome	IG1	IG2	RR (IG1vsCG)	LCI	UCI	RR (IG2vsCG)	LCI	UCI
Bowen†[31]	2007	RI	HE	HHP	0.72	0.54	0.97	0.39	0.27	0.56
Butz[37]	1990	GI	HHP		0.85	0.73	0.99			
Wilson[214]	1991	GI	HHP		0.24	0.1	0.6			
Wilson[214]	1991	SI	HHP		2.18	0.94	5.06			
Kimel[108]	1996	RI	HHP		0.65	0.12	3.48			
Master[130]	1997	RI	HHP		0.96	0.69	1.32			
Master[130]	1997	GI	HHP		0.66	0.37	1.2			
White[211]	2001	RI	HHP		0.72	0.55	0.95			
White[211]	2001	GI	HHP		0.63	0.4	1			
Guinan[85]	2002	RI	HHP		0.75	0.65	0.86			
White[210]	2003	RI	HHP		0.76	0.52	1.11			
Mott†[148]	2007	RI	HHP	HH (ABHS)	0.78	0.7	0.87	0.79	0.71	0.88
Mott†[148]	2007	GI	HHP	HH (ABHS)	0.6	0.39	0.94	0.53	0.33	0.86
Nandrup-Bus[152]	2009	RI	HHP		0.93	0.81	1.08			
Nandrup-Bus[152]	2009	GI	HHP		0.7	0.55	0.89			
Stebbins[187]	2011	ILI	HHP		0.6	0.35	1.04			
Stebbins[187]	2011	Inf. A	HHP		1.65	0.94	2.91			
Stebbins[187]	2011	Inf. B	HHP		0.92	0.76	1.12			
Nicholson[156]	2014	GI	HHP		0.79	0.66	0.94			
Nicholson[156]	2014	SI	HHP		1.32	1.12	1.54			
Priest[162]	2014	GI	HHP		1.03	0.84	1.26			
Wooten‡[215]	2004	SI	PHP	PHP	0.47	0.17	1.32			
Zinderman[216]	2004	SI	PHP		0.6	0.47	0.77			
Romano‡[166]	2006	SI	PHP	HHP	7.47	1.77	31.61	0.52	0.05	5.64
Sanders[172]	2009	SI	PHP		0.7	0.2	2.41			

Study	Year	Outcome	IG1	IG2	RR (IG1vsCG)	LCI	UCI	RR (IG2vsCG)	LCI	UCI
Elias[64]	2010	SI	PHP	Other	0.67	0.35	1.26	1.12	0.65	1.93
Elias[64]	2010	MRSA	PHP	Other	4.95	0.58	42.12	12.58	1.65	95.68
Krilov[113]	1996	GI	DI		0.03	0	0.41			
Bright[35]	2010	RI	DI		0.61	0.34	1.1			
Goldstein[78]	2006	SI	MF		1.36	1.2	1.53			
Goldstein[78]	2006	SI	MF		1.18	1	1.4			
Lee[3]	2010	RI	Other	Other	0.44	0.29	0.69	0.22	0.07	0.68

†Multiple interventions evaluated: IG (Intervention group) RR (risk ratio) Chlorhexidine (CHX); Hand hygiene (HH) with soap (S) antibacterial soap (ABS) or alcohol-based hand sanitizer (ABHS); Personal hygiene promotion (PHP); Hand hygiene promotion (HHP); Multifactorial (MF); Disinfection (DI)

‡Pre and post-test design, evaluated more than one year

Table 5 Unadjusted risk ratios (RR) of GI using hygiene prevention strategies

Author	Year	IG1	IG2	RR (IG1vs CG)	LCI	UCI	RR (IG2vs CG)	LCI	UCI
Black[26]	1981	HW+S		0.66	0.47	0.91			
Han[22]	1989	HW+S		0.78	0.63	0.96			
Shahid[179]	1996	HW+S		0.63	0.55	0.71			
Boulware[29]	2004	HW+S		0.55	0.29	1.07			
Luby[1(125)]	2004	HW+S	Other	0.87	0.70	1.09	0.71	0.52	0.96
Luby[1(125)]	2004	HW+S	Other	0.69	0.56	0.85	0.29	0.20	0.42
Savolainen[174]	2012	HW+S	HS	0.87	0.75	1.01	1.17	1.09	1.27
Larson[117]	2004	HW+ABS		1.01	0.72	1.41			
Hubner[99]	2010	HS		0.53	0.23	1.26			
Prazuck[161]	2010	HS		0.67	0.51	0.89			
Butz[37]	1990	HHP		0.85	0.73	0.99			
Wilson[214]	1991	HHP		0.24	0.10	0.60			
Master[130]	1997	HHP		0.67	0.37	1.21			
White[211]	2001	HHP		0.63	0.40	1.00			
Mott[1(148)]	2007	HHP	HS	0.60	0.39	0.94	0.43	0.27	0.70
Nandrup-Bus[152]	2009	HHP		0.70	0.55	0.89			
Nicholson[156]	2014	HHP		0.79	0.66	0.94			
Priest[162]	2014	HHP		1.03	0.84	1.26			
Apisarnthanarak[1(11)]	2009	IC	Other	0.29	0.24	0.34	0.22	0.18	0.26
Mahooney[126]	1991	HE		0.94	0.62	1.42			

1. Multiple interventions evaluated: IG (Intervention group) RR (risk ratio) Chlorhexidine (CHX); Hand hygiene (HH) with soap (S) antibacterial soap (ABS) or alcohol-based hand sanitizer (ABHS); Personal hygiene promotion (PHP); Hand hygiene promotion (HHP); Multifactorial (MF); Disinfection (DI)

Table 6 Unadjusted risk ratios of RI using hygiene prevention strategies

Study	Year	IG1	IG2	RR (IG1VSCG)	LCI	UCI	RR (IG2VSCG)	LCI	UCI
Castilla[39]	2013	HH (ABHS)		1.19	1.01	1.39			
Larson[117]	2004	HH (ABS)		0.89	0.81	0.98			
Falsey‡[68]	1999	HH (ABHS)		1.21	0.72	2.03			
Falsey‡[68]	1999	HH (ABHS)		0.93	0.60	1.44			
Morton[147]	2004	HH (ABHS)		0.62	0.44	0.89			
Van Camp[197]	2007	HH (ABHS)		1.09	0.07	16.99			
Larson†[116]	2010	HH (ABHS)	Other	0.83	0.77	0.89	1.10	1.03	1.17
Larson†[116]	2010	HH (ABHS)	Other	0.86	0.65	1.13	0.69	0.52	0.93
Larson†[116]	2010	HH (ABHS)	Other	1.15	0.67	1.98	0.96	0.55	1.67
Kimel[108]	1996	HHP		0.65	0.12	3.48			
Master[130]	1997	HHP		0.96	0.69	1.32			
Ryan[169]	2001	HHP		0.55	0.52	0.59			
White[211]	2001	HHP		0.72	0.55	0.95			
Guinan[85]	2002	HHP		0.75	0.65	0.86			
White[210]	2003	HHP		0.76	0.52	1.11			
Mott†[148]	2007	HHP	HS	0.78	0.70	0.87	0.60	0.53	0.68
Nandrup-bus[152]	2009	HHP		0.93	0.81	1.08			
Stebbins‡[187]	2011	HHP		0.60	0.34	1.04			
Stebbins‡[187]	2011	HHP		1.66	0.94	2.94			
Talaat‡[191]	2011	HHP		0.77	0.73	0.82			
Priest[162]	2014	HHP		1.00	0.92	1.09			
Bright[35]	2010	DI		0.61	0.34	1.10			

Study	Year	IG1	IG2	RR (IG1VSCG)	LCI	UCI	RR (IG2VSCG)	LCI	UCI
Bowen(31)	2007	HE	HHP	0.72	0.54	0.97	0.29	0.20	0.43
Lee[3]	2010	Other		0.44	0.29	0.69			

†Multiple interventions evaluated: IG (Intervention group) RR (risk ratio) Chlorhexidine (CHX); Hand hygiene (HH) with soap (S) antibacterial soap (ABS) or alcohol-based hand sanitizer (ABHS); Personal hygiene promotion (PHP); Hand hygiene promotion (HHP); Multifactorial (MF); Disinfection (DI)

‡Outcomes evaluated individually (i.e. Influenza A, Influenza B, ILI, URI)

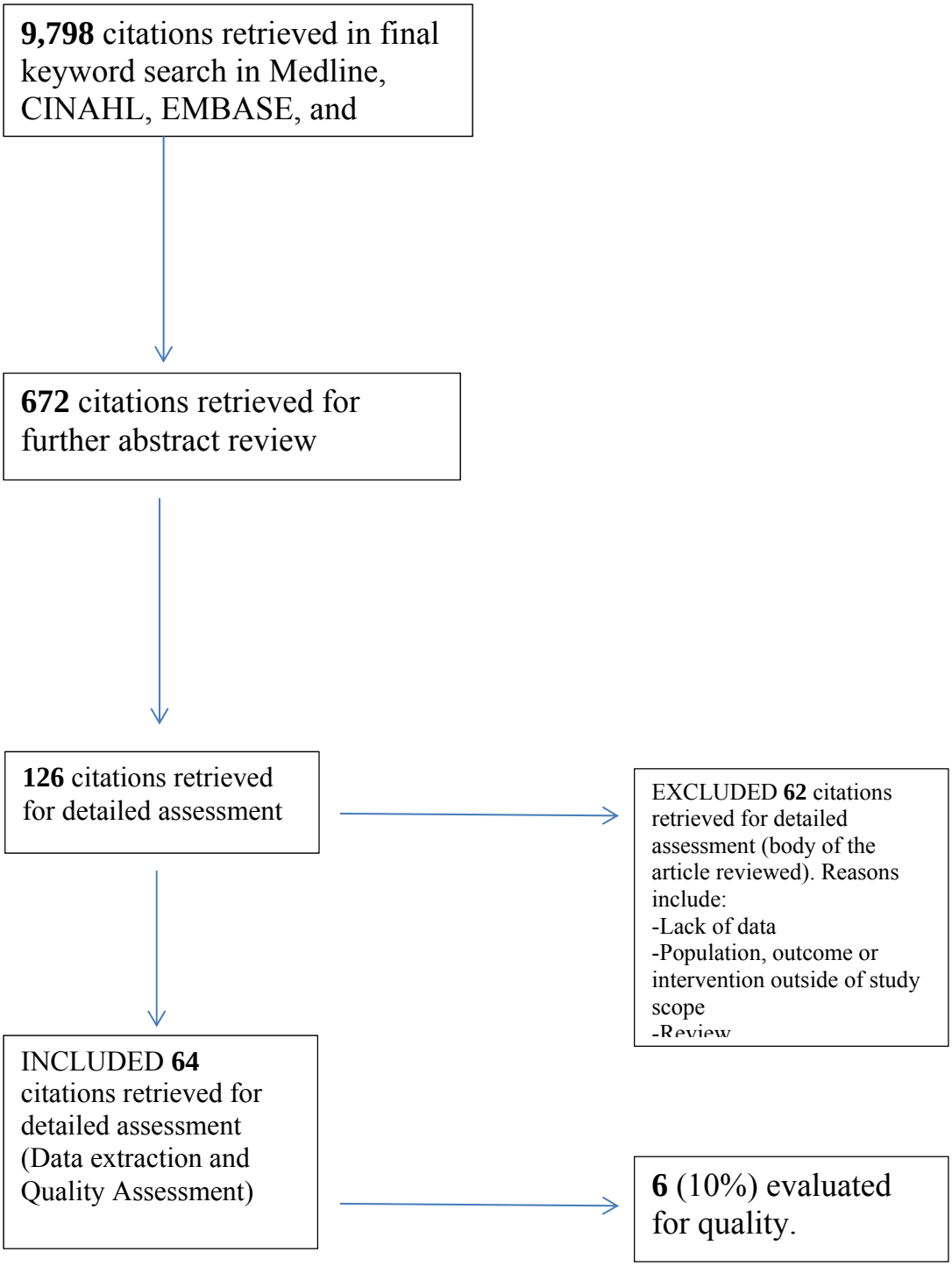
Table 7 Unadjusted relative risks of SSTI and MRSA-associated SSTI using hygiene prevention strategies

Author	Year	IG1	IG2	RR (IG1vsCG)	LCI	UCI	RR (IG2vsCG)	LCI	UCI
Whitman[213]	2010	CHX		1.25	0.86	1.84			
Fritz[75]	2012	CHX		0.78	0.55	1.10			
Fritz[75]	2012	CHX		0.35	0.15	0.83			
Miller[142]	2012	CHX		0.97	0.40	2.36			
Luby[†][123]	2002	HH (ABS)	HH(S)	0.64	0.50	0.85	1.13	0.91	1.42
Larson[117]	2004	HH (ABS)		0.52	0.21	1.29			
Luby[†][124]	2005	HH (ABS)	HH(S)	1.02	0.06	16.23	0.93	0.06	14.9
Wooten[‡][215]	2004	PHP	PHP	0.47	0.17	1.32	0.51	0.05	5.67
Zinderman[216]	2004	PHP		0.60	0.47	0.77			
Romano[‡][166]	2006	PHP	PHP	7.47	1.77	31.61	0.52	0.05	5.64
Sanders[172]	2009	PHP		0.70	0.20	2.41			
Morrison[‡][146]	2013	PHP	PHP	0.98	0.96	1.00			
Morrison[146]	2013	PHP	PHP	0.58	0.54	0.62			
Wilson[214]	1991	HHP		2.18	0.94	5.06			
Nicholson[156]	2014	HHP		1.32	1.13	1.54			
Goldstein[‡][78]	2006	Multifactorial		1.36	1.20	1.54			
Goldstein[‡,§][78]	2006	Multifactorial		1.18	1.00	1.40			
Elias[†,‡,§][64]	2010	Other	IC	0.67	0.35	1.26	1.12	0.65	1.93
Elias[†,‡,§][64]	2010	Other	IC	4.95	0.58	42.12	12.6	1.65	95.7

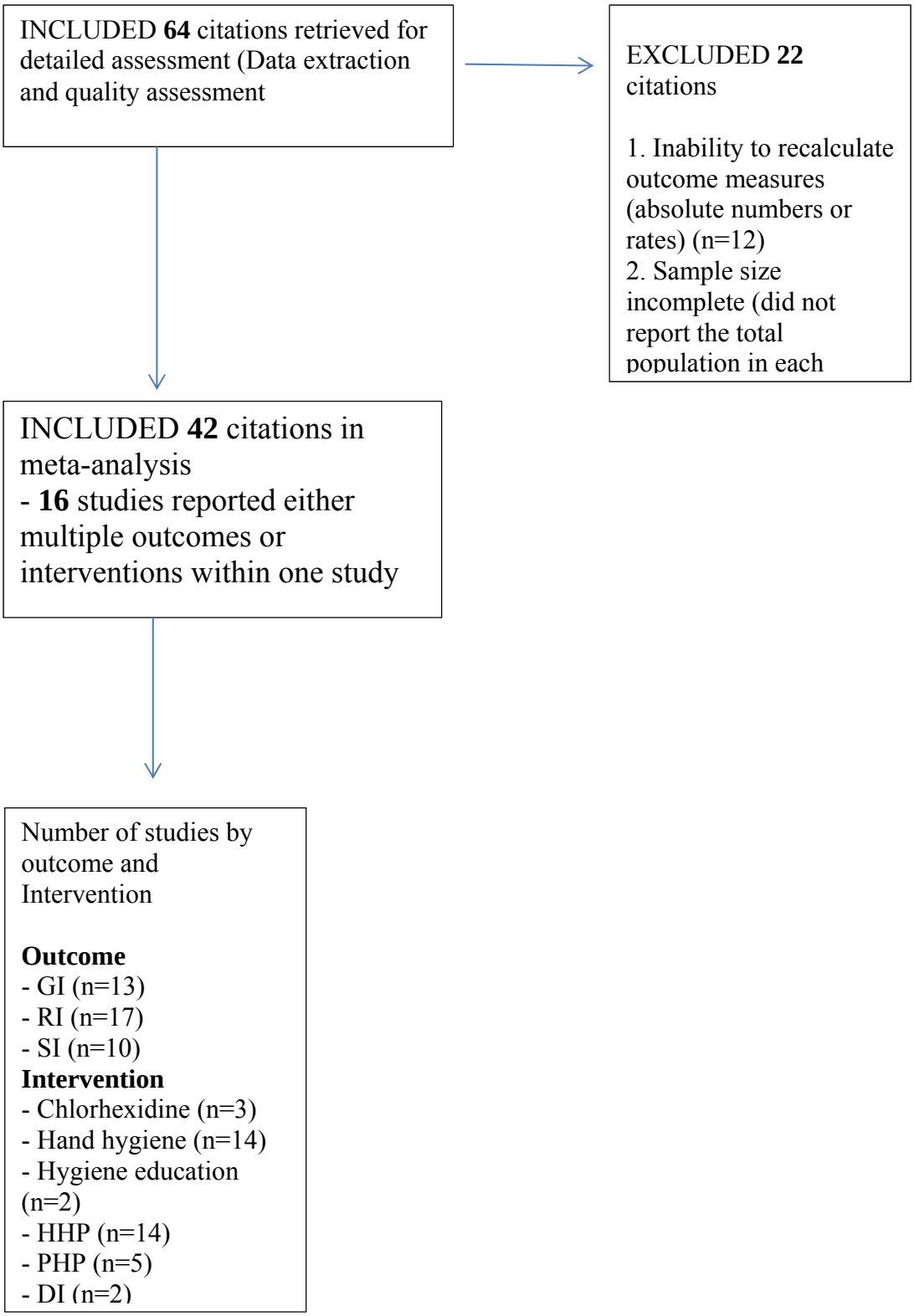
[†]Multiple interventions evaluated: IG (Intervention group) RR (risk ratio) Chlorhexidine (CHX); Hand hygiene (HH) with soap (S) antibacterial soap (ABS) or alcohol-based hand sanitizer (ABHS); Personal hygiene promotion (PHP); Hand hygiene promotion (HHP); Multifactorial (MF); Disinfection (DI); Infection control (IC)
[‡]Evaluated pre-post intervention implementation
[§]Outcomes evaluated individually (SI and MRSA)

Figure 10 Search strategy flow chart

All Studies



Included studies



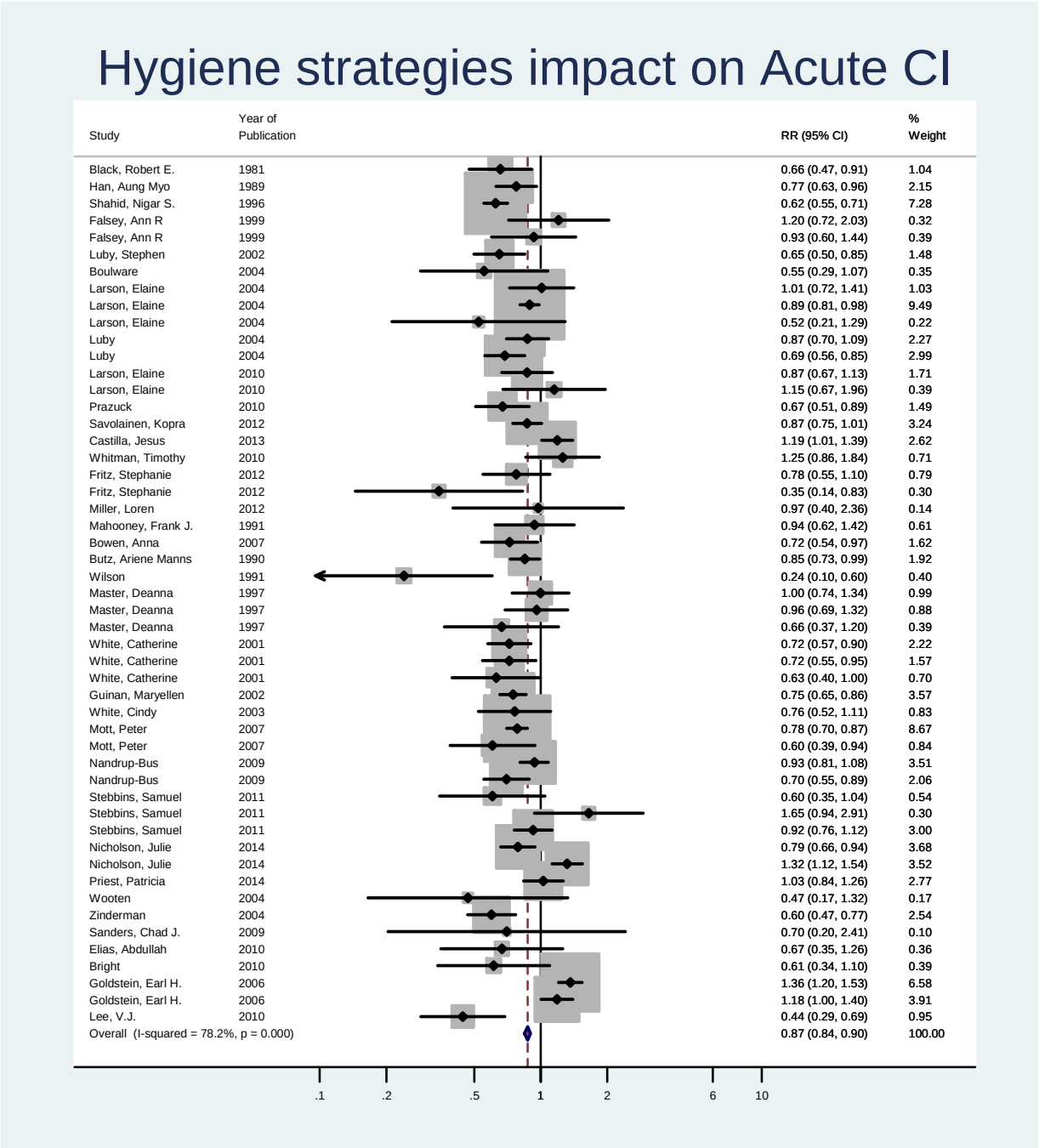


Figure 11 Forest plot of impact of hygiene strategies on acute communicable illness

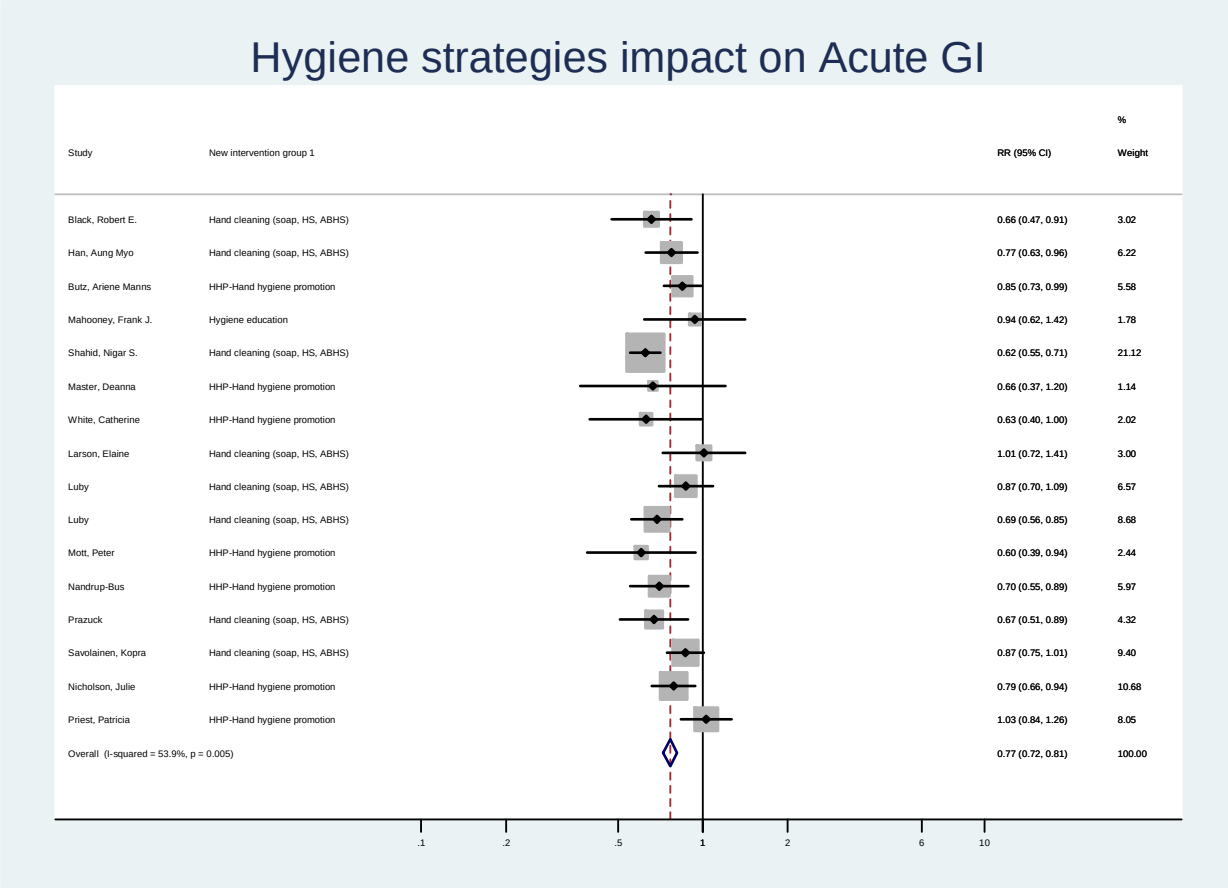


Figure 12 Forest plot of the impact of hygiene strategies on acute gastrointestinal illness

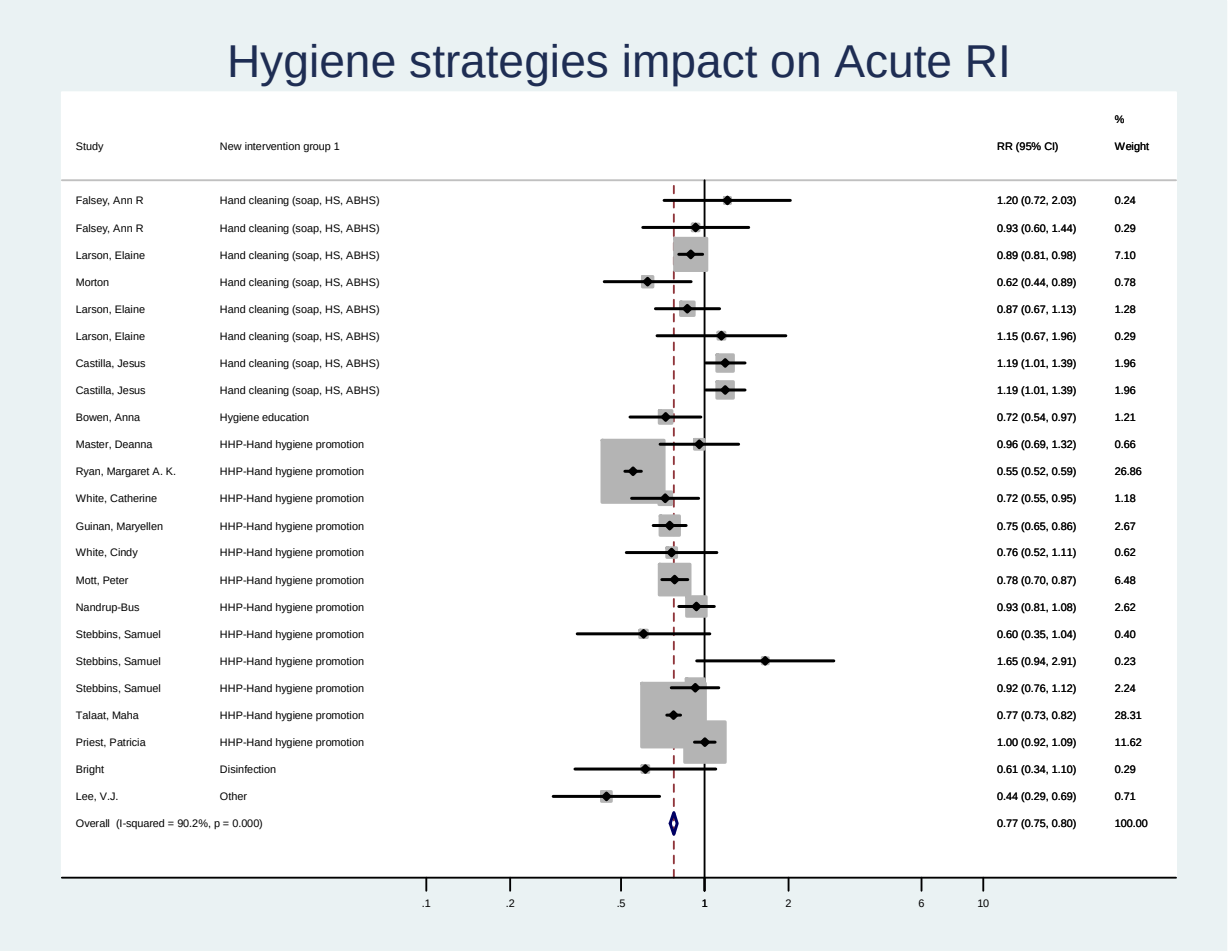


Figure 13 Forest plot of the impact of hygiene strategies on acute respiratory illness

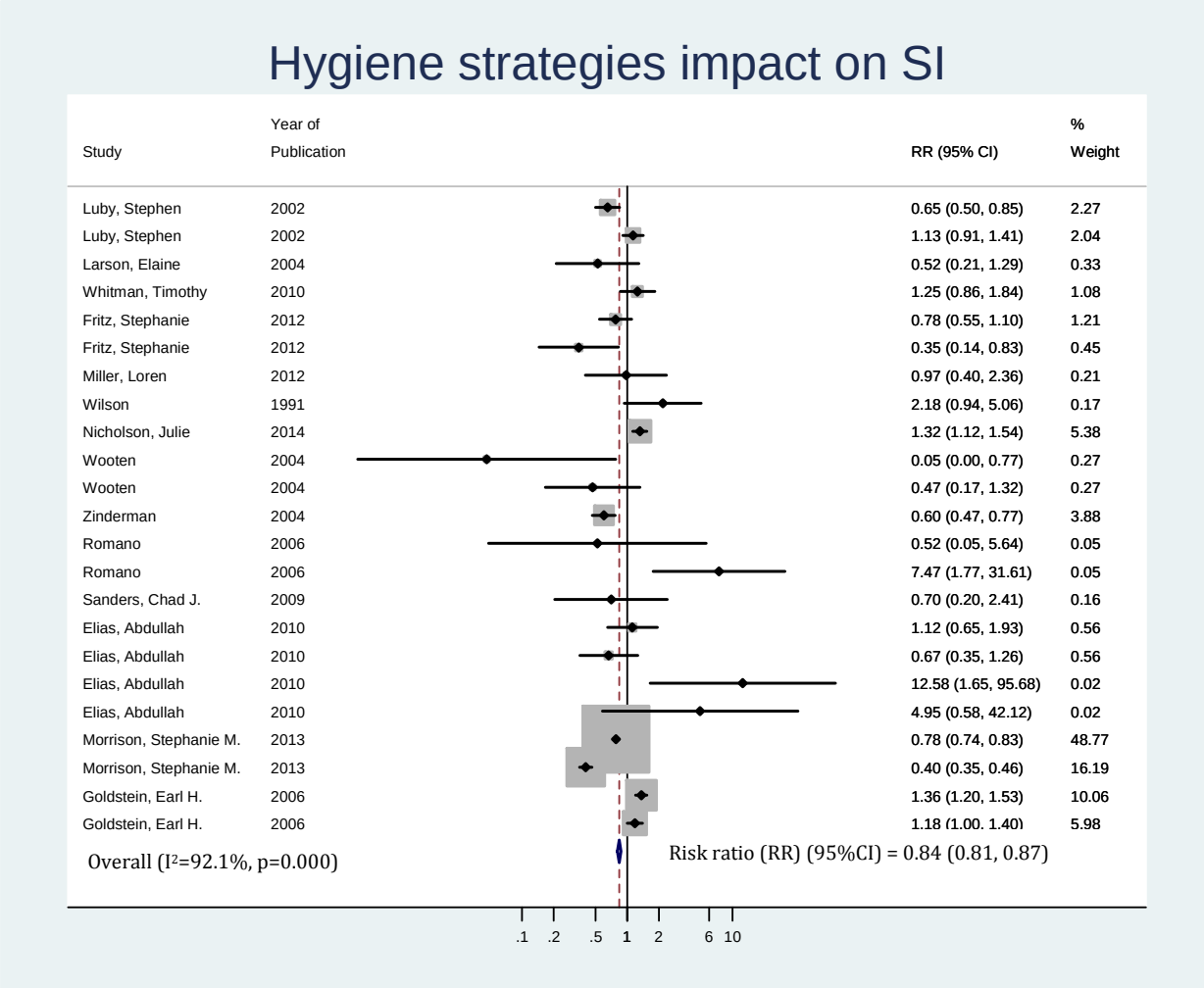


Figure 14 Forest plot of the impact of hygiene strategies on skin infections

Chapter 3: Estimation of Staphylococcus aureus skin and soft tissue infections Lost-time in Training burden among Army Recruit Trainees from 2006 through 2009 (Part 1)

ABSTRACT

Background: Military trainees are known to be at risk for *Staphylococcus aureus* related skin and soft tissue infections. Little is known about the actual burden in terms of lost-time in training in this population.

Purpose: The purpose of this study is to derive estimates of lost time in training burden of overall, *Staphylococcus aureus* and methicillin resistant *Staphylococcus aureus* SSTI in the active duty military trainee population.

Methods: Existing military health system datasets were used to conduct a retrospective, descriptive study, not involving human research, to assess the SSTI and MRSA SSTI lost-time in training burden among the Army active duty recruit trainee population visiting military treatment facilities during training for care at five Army Training Installations from 2006 to 2009. Demographic and medical information were obtained from three military health system data sets. Burden was measured in term of lost time in training which encompasses time factors associated with clinic visits, emergency room and hospital visits as well as sick in quarters and limited duty dispositions, and being recycled from training. Rates of overall and MRSA SSTI were calculated as new infections per 100 recruit trainee cycles. SSTI was assessed by using ICD-9-CM codes (e.g. 680-686 and 704.8). MRSA isolates were identified by clinical culture information.

Results: A total of 20,884 overall SSTI, 14,243 *S.aureus* and 9,552 MRSA SSTI were found among recruit trainees at the five Army training installations from 2006 through 2009. During the study period, overall, *S.aureus* and MRSA SSTI rates were 215.4, 146.9 and 98.0 infections per 100 training-cycles, respectively. Approximately 73,000 training days were lost because of SSTI during the four year study period (median

=2.00 (IQR: 3.00days); range 0.50-102.5 days). Univariate analyses revealed significant differences ($p<0.001$) between overall, *S.aureus,* and MRSA SSTI lost-time in training and host-specific factors (sex, marital status, training location, and military occupational specialty), temporal factors (phase of training and year of event); initial clinical care (I&D procedure and MRSA coverage); and microbiology (culture acquisition and resistance to oxacillin). The final multivariate negative binomial regression model showed clinical outcomes (microbiology and syndrome); initial care (MRSA coverage, I&D procedure); temporal factors (training phase, season, year of infection); and training location were all associated with overall SSTI related lost-time in training burden ($p<0.001$).

Conclusions: Understanding the overall, *S.aureus* and MRSA SSTI lost time in training burden among recruit trainees is important. This is the first study that attempts to evaluate burden in terms of time as opposed to only rates. Furthermore, rates calculated are based on a person's time in training which seems more relevant to this population and could be easier to apply at the operational level. This study found that many factors contribute to the overall lost-time in training burden in this population such as having a complication which could lead to training remediation, initial clinical care, phase of training in which the infection occurred, and the training site. The information found from this investigation can be used to direct economic analyses.

INTRODUCTION

Background

Military trainees are known to be at high-risk for skin and soft tissue infections (SSTI) such as cellulitis and abscess, and a significant proportion of these infections are caused by community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA).(40; 216) Outbreaks of MRSA-associated SSTI have been well described in military settings, but less is known about the burden of these infections on the military healthcare system. (8; 9; 28; 51) Disproportionately higher rates of overall and MRSA-associated SSTIs among military training populations can result in an increased health care burden and impairment in the ability of soldiers to participate in and successfully complete training programs.

Previous studies

Surveillance reports published from 1998 through 2006 showed an increase in the overall incidence for cellulitis and abscess increased among active duty military service-members. Most of the cases and the highest rates were among military installations that conducted training for active duty recruits. (8; 9) Additionally, as of 2014 there were over 1,415,806 medical encounters, approximately 782,616 individuals affected, and approximately 94,050 hospital bed days for skin disease (not contact dermatitis or sebaceous gland disease). (17; 19) Among U.S. military recruits (defined as active component members of the Army, Navy, Air Force, or Marine Corps with enlisted ranks of E1 [Private] to E3 [Private First Class] who served at one of the nine training locations) skin infections ranked 4th behind respiratory infections, injury, and the

signs/symptoms disease burden categories in terms of medical encounters (≈20, 000) and individuals affected (≈12, 500). (18)

In the Army specifically, those recruits waived for unspecified skin problems all had higher levels of attrition over time than their matched comparison counterparts. (157) Niebuhr et al (2003) reported that unspecified skin conditions accounted for 4% of hospital admissions within the first year of service from 1996 to 2001. This is important, considering hospitalization is deemed a precursor for attrition within the first year of service. (157)

Finally, a descriptive study conducted from 2002 through 2007 among Army active duty service members at an Army training installation, reported trends in MRSA-associated infections. Over 3,000 infections were observed. Annual rates of CA-MRSA peaked around 41.4 cases per 1,000 soldiers in 2005. Approximately10% of cases required hospitalizations. Over 70% of the cases were assigned to a training unit. Additionally, 39% of infections resulted in a limited duty disposition. (118; 144)

A comprehensive evaluation of the burden of SSTIs in the active duty military trainee population has not been done. A re-evaluation is warranted because although a recent surveillance report was published regarding skin infections in the Armed Forces, it does not focus specifically on the Army Active Duty trainee population, especially with regards to MRSA SSTI nor burden associated with lost-time in training.(13) Multiple uncertainties still exist regarding the burden of SSTI and CA-MRSA-associated SSTI in the active duty military recruit trainee population, the burden in certain trainee subpopulations (e.g. rank and assigned duty station), and health care utilization among trainees diagnosed with an SSTI (e.g. visits to the physician, antibiotics prescribed,

procedures done, etc.). Previous studies have tried to elucidate these uncertainties, but questions remain. The use of a combination of data sources, including patient, pharmacy, and microbiologic, could assist in the evaluation of the burden of SSTI and MRSA-associated SSTI in the active duty military trainee population.

The primary objective of this study is to evaluate the burden related to SSTI and MRSA-associated SSTI among the active duty Army training population from 2006 through 2009, specifically lost time in training. The specific aim of this study is to evaluate not only the burden of overall and MRSA SSTI in terms of rates but to study the lost-time in training (LTT) burden and its associated factors. This would be the first attempt at evaluating the operational burden in terms of lost-time in training due to overall and MRSA SSTI.

METHODS

This descriptive burden study is a retrospective cohort evaluation. Existing de-identified military health data were used to assess the burden of SSTI and MRSA-associated SSTI among active duty military recruit trainees visiting military treatment facilities (MTFs) from 2006 through 2009. This study [**IDCRP-066**] was approved as exempt by the Uniformed Services University of the Health Sciences Infectious Disease Institutional Review Board on 10 February 2012 and approved by the Army Institute of Public Health.

Study population

The population of interest was the active duty recruit trainee population. In order to arrive at this specific population, multiple steps were taken. The study population was drawn from a cohort of Army active duty service-members identified in the Defense Manpower Date Center (DMDC) database with training entry dates from 2006 through 2009 **(Figure 15)**. Once this cohort was identified, the cohort was filtered to only those Army service-members with a DMDC Unit Identification Code (UIC) based on the five Army One Stop Unit Training (OSUT) sites. These sites are located in Fort Benning, Georgia; Fort Jackson South Carolina; Fort Leonard Wood, Missouri; Fort Sill, Oklahoma; and Fort Knox, Kentucky.

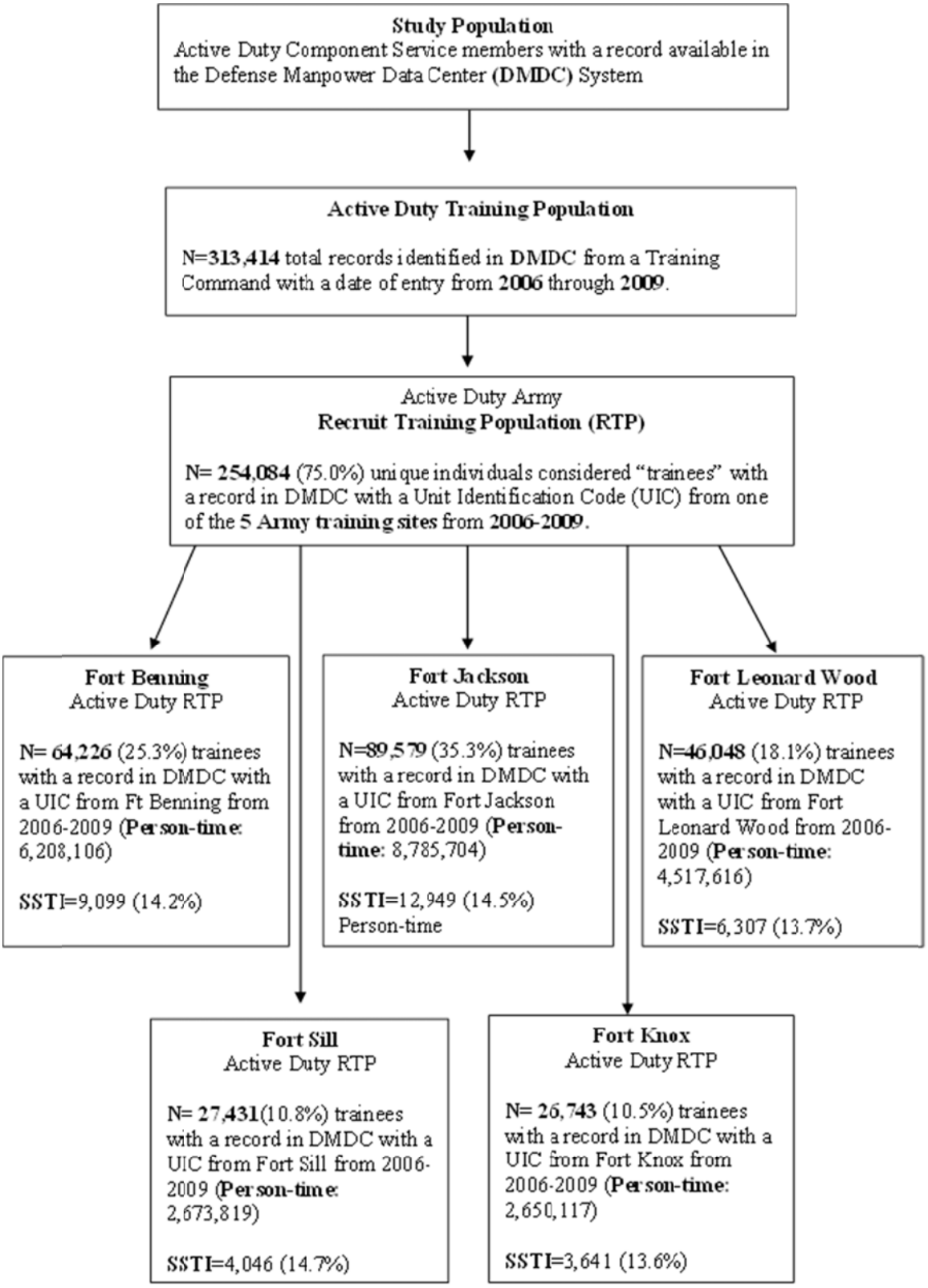


Figure 15 Study population flow chart

The study population was narrowed further to only recruit trainees (**Figures 16a and 16b**). For the purposes of this study, recruit trainees were defined as Army active component service members with a rank of E1 to E4 who served at one of the five Army One Stop Unit Training (OSUT) locations during an Army-specific training period following a first ever service record. (18) These records were identified through the DMDC database. The training specific time period was calculated as 105 days from date of entry up to the date of departure. This time-period estimate is based on previous knowledge that OSUT training lasts on average 98 days ±7 days.

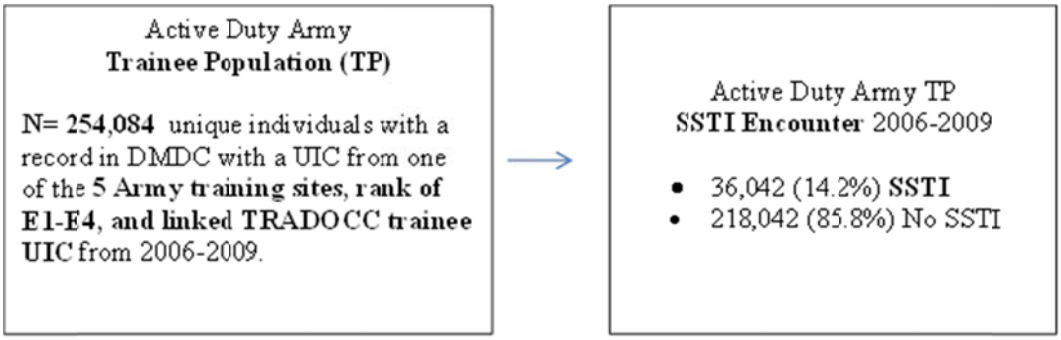


Figure 16a Trainee population

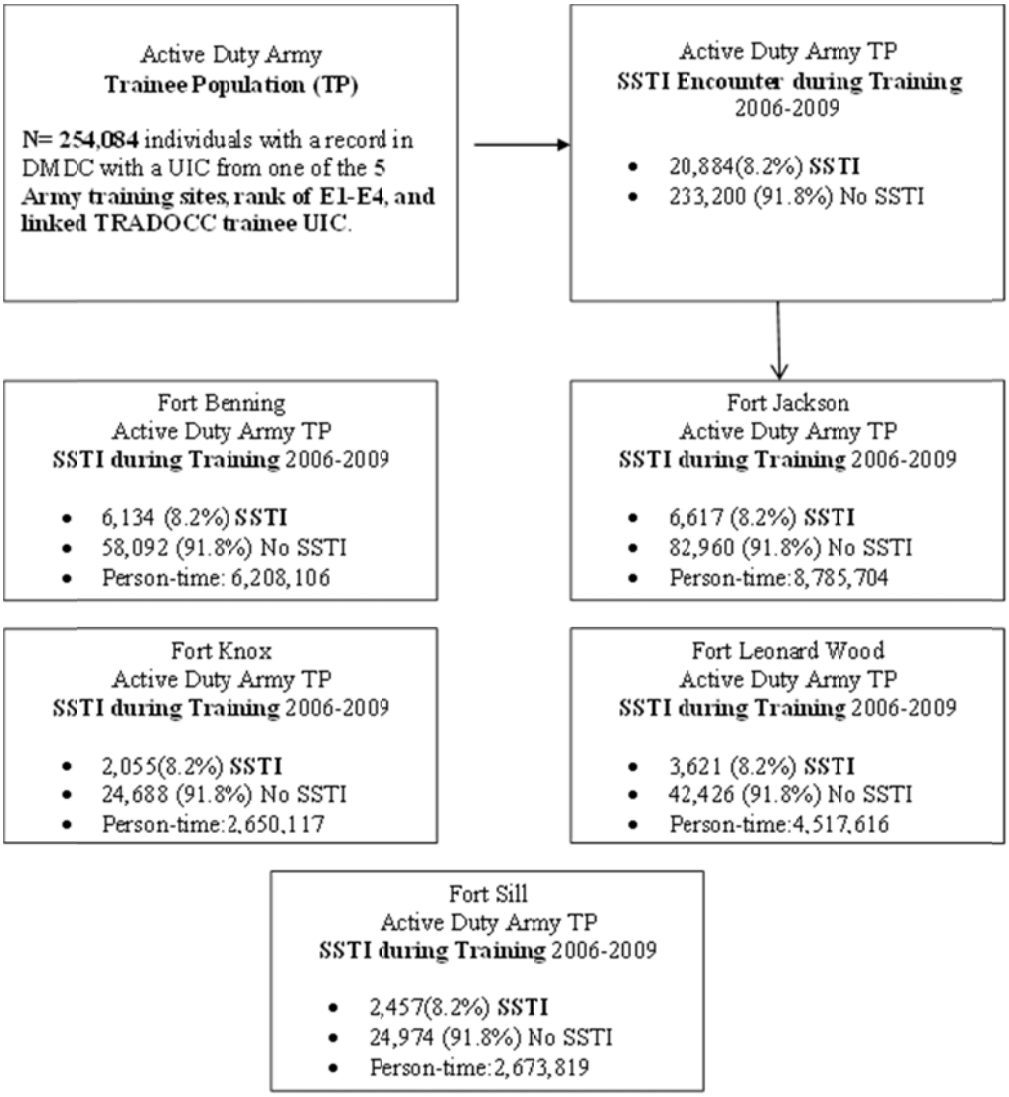


Figure 16b Trainee population flow chart by training site

Data sources

Multiple data sources were used to conduct this analysis. Primarily, military health systems (MHS) datasets were provided to examine disease, procedure, and prescription information. Data were supplied from the US Army Institute of Public Health and the Navy and Marine Corps Public Health Center (NMCPHC), Epidemiologic Data Center (EDC). Data Use Agreements were approved on 9 December 2011. Datasets were retrieved from the Military Data Repository (MDR), Military Health System (MHS)

Mart (M2) and Defense Health Services System (DHSS) Health Level 7 (HL-7). M2 data were used to acquire outpatient and inpatient diagnostic information on Army active duty recruit trainees presenting to their military treatment facility (MTF) for an SSTI. M2 data also provided information, healthcare utilization (clinic encounters, hospitalizations, procedure codes, pharmaceutical information, etc.) and information on patient disposition such as assignment to quarters or released with limitations status. HL-7 was used to identify microbiologic results of SSTIs that were cultured for *Staphylococcus aureus* and antibiotic susceptibility information. Last, DMDC datasets included service-member arrival dates which assisted in determining person-time estimates for overall and MRSA SSTI rate calculations (i.e. cases per 100 training cycles).

Case definitions

Training time

For person-time calculations and to determine whether the infection occurred while in training, a training-specific time period was used. In the case of these 5 training installations, training was estimated to last approximately 14 weeks with a seven day window for in-processing. Therefore, at most, trainees are expected to be at a trainee installation for105 days. If a person was discharged from training or was diagnosed with an infection before completing the full 105 day cycle, the difference between the dates of discharge (or infection event) from the date of entry was used as person-time.

SSTI and MRSA-associated SSTI

Confirmed SSTI cases were defined by ICD-9-CM codes 680-686.8 which are categorized under “Infections of the Skin and Subcutaneous Tissue”. These codes include: 680-680.9 “carbuncle and furuncle”; 681-681.9 “cellulitis and abscess of finger

and toe"; and 682-682.9 "other cellulitis and abscess". SSTI were further classified into two categories, purulent (P) and non-purulent (NP). The definition for a purulent SSTI included a "cellulitis and abscess" diagnosis with a culture, "abscess" manifestation or an "incision and drainage" procedure with MRSA coverage or folliculitis, carbuncle/furuncle, or pilonidal cyst with abscess diagnosis.(65; 203) Non-purulent SSTI were defined as infections lacking abscess-like manifestations, procedures indicative of abscess, and no MRSA coverage. (44; 61; 87) Diagnosis codes for impetigo, pyoderma, felon, acute lymphadenitis, other specified local infections of skin and subcutaneous tissue, and other local infections of skin and subcutaneous tissue were included in this category. Additionally, the SSTI must have occurred while in training; therefore, those infections falling outside of the 105 day training window were not included in this analysis. An initial SSTI case was defined as the first instance of an SSTI diagnosis. The primary diagnosis was evaluated 30 days prior to initial diagnosis and 30 days after initial diagnosis to assess whether the case was new or if it was a follow-on case. A case of SSTI was deemed new if the diagnosis was for a new body location and separated in time (30 days). Cases were considered as "follow-up" if the same diagnosis is observed within the 30 day window. (9; 46; 144)

Persons were identified as having confirmed MRSA-confirmed SSTI if they met the following criteria (1) have a *S. aureus* culture confirmed positive (2) confirmed resistance towards oxacillin or otherwise confirmed as MRSA by clinical microbiology. Persons were matched with available microbiologic cultures based on the specimen type (wound or blood), organism type, and the date of culture. Additionally, pharmacy data was matched based on diagnosis and culture dates (within 10 days of the diagnosis and

culture). These methods were used in previous studies using the data sources that will be used in this study. (46; 144)

To analyze the potential cases of *S.aureus* that might have been missed because infections were not cultured, "*S.aureus*-probable" and "MRSA-probable" variables were created. All assumptions were based on a literature review, a prospective trial at Fort Benning, Georgia [**IDCRP-055**], and internal estimates generated from the military health systems (MHS) data obtained from this current study [**IDCRP-066**].(13; 44; 61; 65; 87; 114; 118; 144; 146; 203) The table below shows the estimates used and their corresponding references. Culture (Cx), Incision and drainage (I&D), *S.aureus* (SA) and MRSA rates were considered in the calculation. Estimates obtained from MHS were considered first in the algorithm. If information was missing, the estimates derived from IDCRP-055 were used. Lastly, the estimates obtained from the literature review were used if information was still needed.

	Literature review		Fort Benning[65] [**IDCRP-055**]		BOI [**IDCRP-066**]	
	P (%)	NP (%)	P (%)	NP (%)	P (%)	NP (%)
Cultured (Cx)	23, 30[146; 203]	NA	87	0	21	19
Incision & Drainage (I&D)	43[144]	16[44; 87]	99	1.2	14	18
S.aureus (SA)	37,55[114; 203]	17, 30, 50[44; 61; 87; 203]	85	0	88	83
MRSA	55,60,70[118; 144; 203]	6.0[61]	65	0	69	60

Using the information in the above table, estimates were derived to calculate probable *S.aureus* (SA-P) and MRSA (MRSA-P) cases along two infection pathways- purulent (P) vs non-purulent (NP). The figure below depicts the pathway. Each branch of

the pathway accounts for the proportion (%) of the infections that were cultured (CX) as well as had an incision and drainage (I&D) procedure. The proportions were applied to the MHS datasets to derive the *S.aureus* probable and MRSA probable estimates. A variable was then created in the MHS dataset that combined confirmed and probable cases (with confirmed cases considered first and then probable cases).

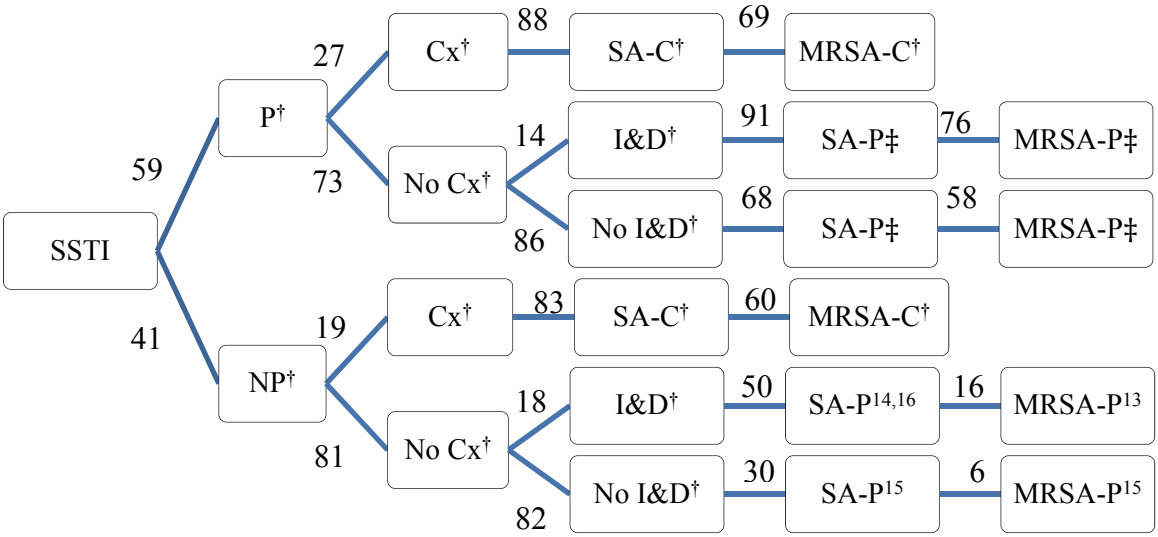


Figure 17 Staphylococcus aureus (SA) and MRSA flow diagram. Point estimates (%) are shown along each branch of the pathway. †MHS data (IDCRP-066), ‡Fort Benning Study (IDCRP-055)

Disease and burden outcomes

The primary outcomes of interest included the incident cases and rates of overall and *S.aureus,* MRSA SSTI. Rates were calculated as one or more infections per 100-training cycles (**appendix F**). The rate's numerator was composed of the number of infections. If an individual had more than one infection, the infection was only counted once in the numerator. The denominator consisted of person-time in training. An individual could have a max of 105 days of person-time. The multiplier was 100 training-cycles (TC). One TC is equivalent to 105 days in training.

Additionally, the lost time in training (LTT) of overall, *S.aureus* and MRSA SSTI was also of interest. Lost time in training was calculated as the amount of time spent away (days) from training in order to receive care during a medical encounter (i.e., clinic, ER, or hospital visit) as well as being assigned to limited duty or 'sick in quarters' status, or being recycled from training. (1) Army regulations state that a recycle is "Any soldier who is delayed in the completion of training due to repeating certain phases of training. This includes personnel delayed for medical reasons…" (AR 612-201-24 February 2011).(21) Additionally, the trainee with an infection, must have spent greater than three days in the hospital after being diagnosed with an SSTI. Using a conservative approach we estimated that lost-time for a recycle is equivalent to the sum of the length of stay in the hospital, 30 days convalescent leave, and 14 days for training remediation. This estimate is based on Army training doctrine and regulations (TRADOC Regulation 350-6) as well as clinical experience.(48) Complete calculations and assumptions can be found in **appendix F**.

Data analyses

Descriptive analyses

All descriptive analyses were performed through SPSS 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Descriptive analyses were performed to measure the distribution and trends of lost-time in training burden among study population characteristics (age, sex, training site, phase of training, rank, ethnicity, etc.). Case demographics were based on a given individual's first presentation. Proportions were used to summarize categorical variables (e.g. sex, ethnicity, marital status, pay grade, rank, service, trainee status). For continuous variables

(e.g. age, number of clinic visits, number of hospital visits, length of stay, the number of antibiotics prescribed) descriptive statistics including mean, median, standard deviation (SD), inter-quartile range (IQR) and 95% confidence intervals (CI) were measured. Annual and seasonal trends of overall, *S.aureus* and MRSA SSTI rates and LTT were also evaluated and were calculated as number of incident overall, *S.aureus* or MRSA SSTI per 100 training-cycles (TC).

Inferential analyses

To measure differences between the binary outcome [e.g. SSTI, yes/no *S.aureus*-confirmed SSTI, or MRSA-confirmed SSTI (yes/no)] and categorical variables (gender, age, training location, etc.) the χ^2 test was used. Differences in rates of overall, *S.aureus* and MRSA-confirmed SSTI among demographic categories were measured using Poisson regression since count data were used.(97) To measure potential differences between lost-time in training (LTT) and categorical variables, Mann-Whitney U or Kruskal Wallace tests were used (variable dependent).(54) All tests were considered significant at $\alpha<0.05$; 95% confidence intervals (CI) were also generated.

Further multivariate analyses performed used a generalized linear model (GLM) with a negative binomial distribution using a log-link function.(23; 76; 96; 97) The GLM was used because it offers a variety of distributions and link functions to choose from when the outcome variable has a non- normal distribution and the outcome is not linearly related to the covariates.(23; 76) In this study, the outcome variable (lost-time in training) does not follow a normal distribution and is based on count data (number of days lost per trainee). Because the distribution of the dependent variable (LTT)was highly skewed and over-dispersed (variance much larger than the mean), the negative-binomial distribution

with log-link function was chosen to adjust for over-dispersion.(96; 97) A log-link function was chosen because the covariates have a non-linear effect on the dependent variable and facilitates interpretation as opposed to log-transforming the dependent variable. (76) The model covariates act multiplicatively on the dependent variable (a % increase in the mean LTT per unit increase in the covariate).(23) Lastly, these methods have been used to perform analyses on similar data. {Group, #134} Multivariate analyses intended to evaluate the relationship between lost-time in training and host-specific factors (sex, training location, and rank); temporal factors (phase of training); initial clinical care (MRSA coverage); syndrome (abscess-cellulitis-like diagnosis); and microbiology (clinical culture). Variable selection into the model was based on clinical importance as well as results from the univariate analysis. A backward method was used to determine the importance of the variables in the model.(83; 97) Multiple methods were used to determine the models fit. The scaled deviance "ratio of the deviance value to its degrees of freedom" was used. If this value was close to 1, the model was deemed to fit well.(76; 83; 97) Additionally, scatter plots of the predicted mean by the standardized deviance residual were used to inspect outliers potentially affecting the model's fit.(23; 83) All tests were considered significant at $\alpha<0.05$; 95% confidence intervals (CI) were also generated. See **appendix F** for a complete description of the model.

RESULTS

Active duty, recruit training population

A total of 254,027 Active Duty Army recruits were included in the training population (**Figure 16b**) from 2006 through 2009. When evaluated by year, the number of recruits entering training remained relatively stable each year [2006=62,149 (24.5%),

2007=58,479 (23.0%), 2008=68,516 (27.0%), and 2009=64,880 (25.5%)] with a slight decline in 2007. One Stop Unit Training (OSUT) lasts approximately 98 days ± 7days. A total of 24,835,362 person-days in training were calculated over the entire four-year study period for the entire training population. Average person-time trended slightly higher in 2006 (99 days per trainee) compared with subsequent study years (approximately, 97 days per trainee).

Study population demographics

Overall, the study population consisted of Caucasian (78.1%), males (83.7%), ages 17-24 years of age (84.4%). Most recruit trainees were single (80.2%). Most recruit trainees identified were assigned to Fort Jackson, SC (35.3%) with Fort Benning, GA following second most frequent (25.3%). Almost half of the population had the lowest military rank for entry into military service (44.6%). Approximately 17% of trainees had "infantry" listed as their military occupational specialty. Other occupations included logistics (11.5%), communications (7.6%), and field artillery (6.5%). **(Tables 8 and 9)**

Demographic variables were further evaluated by those individuals in the recruit trainee cohort with a diagnosis of SSTI and those who did not have a diagnosis for SSTI. Analyses showed significant differences existed among sex, race, marital status, rank, MOS, and training location (all $p<0.001$ respectively). All values are shown in **tables 8 and 9.**

Disease outcomes

A total of 20,884 incident SSTI cases as well as 4,154 and 2,819 incident S.aureus and MRSA-confirmed-SSTI cases occurred among the recruit trainee population during training from 2006 through 2009. Persons in the study cohort were observed on more than one occasion for an SSTI because of a new infection; therefore, the total number of infections observed during the study period was 27,919 (approximately 5,000 trainees had a repeat infection (mean 1.34 infections ±0.69; range: 1-7) (**Table 10a and Figure 16b**). SSTI with positive *S.aureus* cultures totaled 4,154 (19.9%) with 547 repeat infections. Likewise, there were 2,819 (67.9%) incident infections with positive cultures for *S.aureus* with resistance towards oxacillin (Methicillin Resistant *Staphylococcus*

aureus; herein, known as MRSASSTI), 175 (6.4%) of which had repeat infections. Probable cases of *S.aureus* and MRSA were also estimated to identify potential cases missed because of non-culture. Approximately 23% of SSTI overall [purulent (27%) and non-purulent (19%)] were cultured which contributed to a potential gross underestimation of *S.aureus* and MRSA SSTI cases. Based on literature review and internal estimates, total of 10,089 and 6703 *S.aureus* and MRSA-probable cases were calculated, respectively (**Table 10a and Figures 17a-e**). Throughout the remainder of this study, the combined *S.aureus* and MRSA SSTI confirmed and probable estimates were used for all subsequent calculations related to these variables (i.e., proportions, rates, and lost-time in training). The overall SSTI rate among trainees with an infection during training was 215 infections per 100 training-cycles (TC); while *S.aureus* and MRSA-confirmed SSTI rates were 41.8 and 28.0 infections per 100 TC (respectively) over the entire four year study period. Rates of *S.aureus* and MRSA-probable SSTI were 104.1 and 69.1 per 100 TC, respectively (Table 3.2a). In total, there were 14,243 *S.aureus* cases (146.9 per 100 TC) and 9,522 MRSA SSTI cases (98.0 per 100 TC).

Rates of overall, *S.aureus* and MRSA SSTI were explored by demographic variables. Significant differences were found among rates for SSTI overall among the race, installation, and military occupational specialty (MOS) variables. Rates were significantly greater among African Americans compared with Caucasians for those with SSTI overall ($p<0.05$) as well as *S.aureus* and MRSA SSTI ($p<0.05$ and $p<0.001$, respectively). (**Table 8.0**) When compared with Fort Benning, the training sites of Fort Leonard Wood ($p<0.01$) and Fort Sill had significantly higher rates of SSTI overall ($p<0.01$ and $p<0.001$) and MRSA SSTI ($p<0.05$ and $p<0.01$, respectively). Significantly

higher *S.aureus* SSTI rates were found among those attending training at Fort Sill compared with Fort Benning ($p<0.001$). (**Table 9**) When compared to the infantry MOS, all other MOS types (except Armor) had significantly higher rates of SSTI overall and *S.aureus* SSTI. Significantly higher MRSA SSTI rates were found among logistics, medical, communications and armor occupational specialties when compared to the infantry MOS. (**Table 9**)

Annual rates of overall, *S.aureus*, and MRSA SSTI peaked in 2008 with 218.8, 151.0, and 99.3 and infections per 100 TC, respectively. Although not found to be significantly different, results showed a slight decline in overall SSTI rates from 2008 to 2009; this trend was also observed among *S.aureus* and MRSASSTI rates (**Figure 18).** Evaluation of absolute number of overall and MRSA SSTI cases by month and year shows a consistent trend, with the lowest number of cases being in the winter months and the highest number of cases being during the summer months. Peak rates for overall SSTI seemed to follow the same trend (**figure 19**), but peak rates for MRSA SSTI occurred in February of each subsequent year after 2006 (**figure 20**).

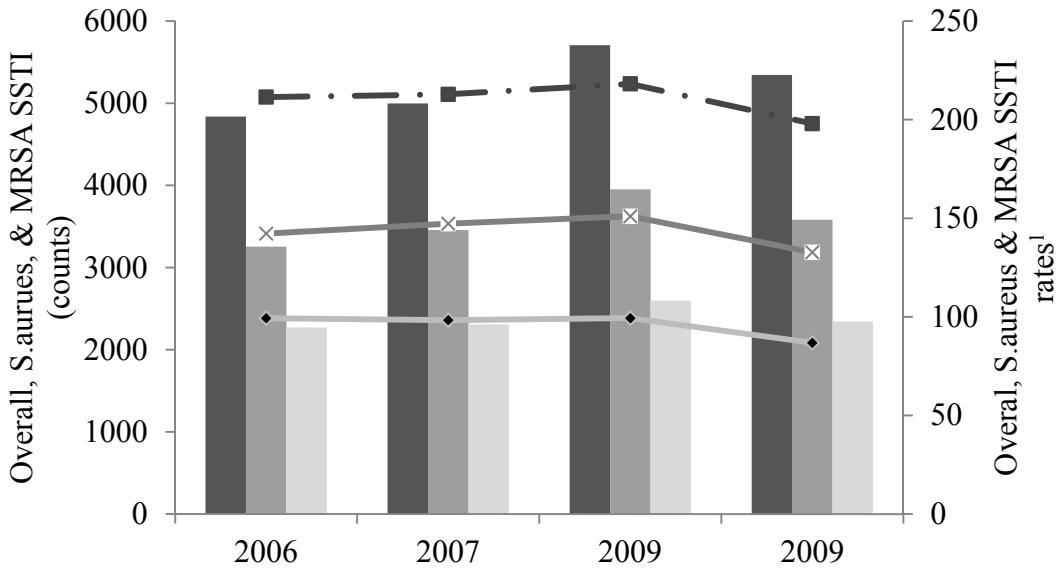


Figure 18 Total number of overall, S.aureus and MRSA SSTI cases (black, light grey and dark grey bars) by year. Additionally, provides total overall, *S.aureus,* MRSA-confirmed SSTI rates (depicted by black dashed lines (squares), dark grey dashed lines (crosses), and light grey line (diamonds), respectively). [1]Rates are calculated as one or more infections per 100 training-cycles. A training cycle is equivalent to 105 days.

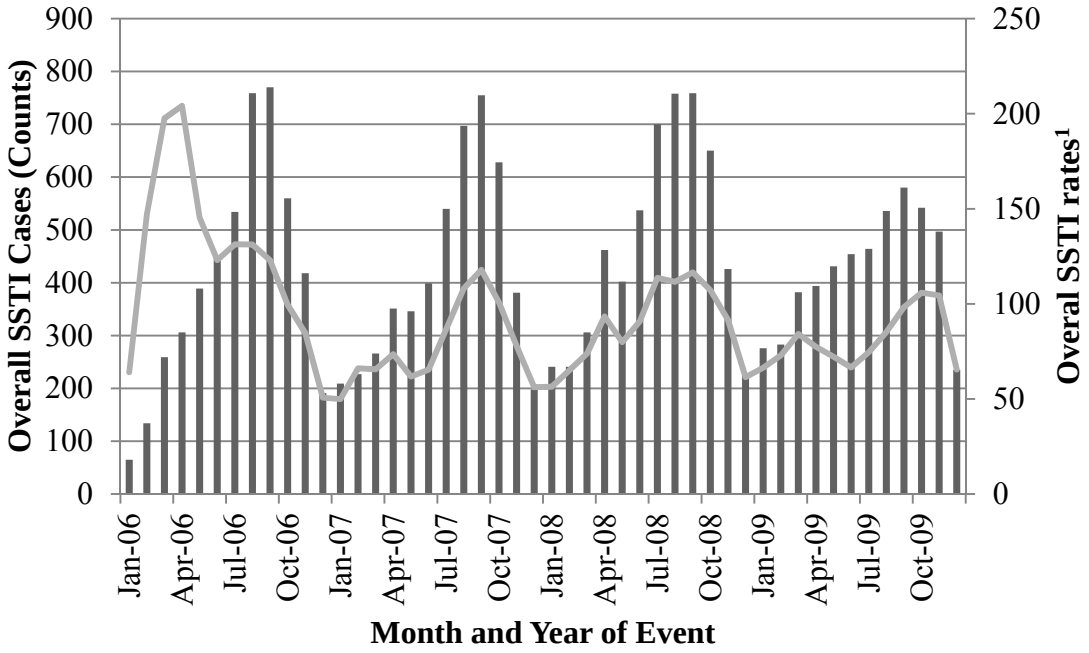


Figure 19 Overall SSTI incident infections and rates by month and year. [1]Rate is equivalent to one or more SSTI cases per 100 training cycles. One training cycle consists of 105 days. Grey bars represent overall SSTI cases while the black line represents the overall SSTI rate.

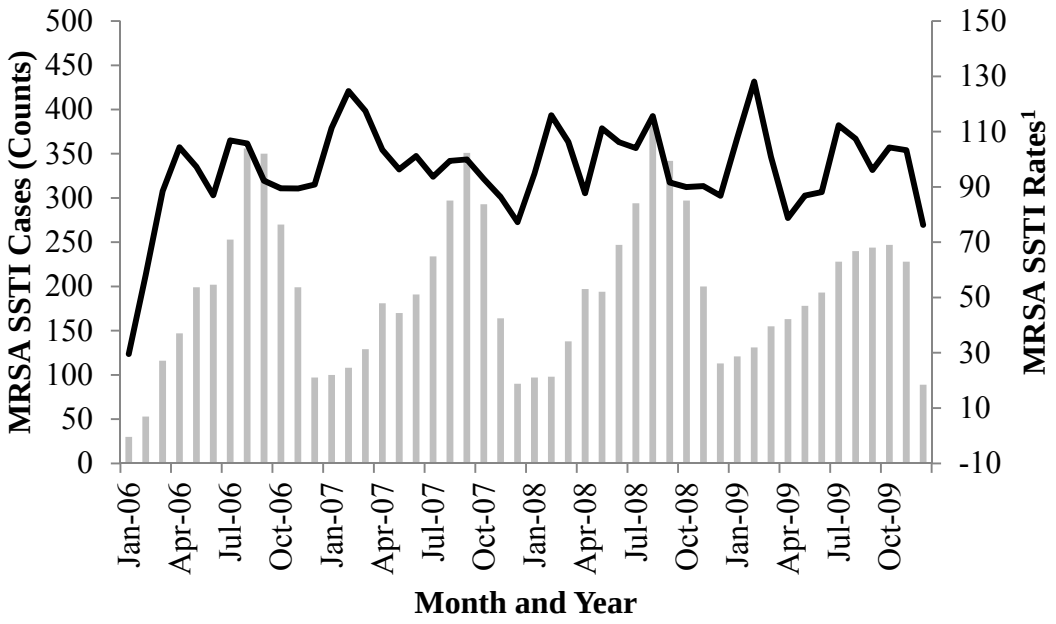


Figure 20 MRSA SSTI incident infections and rates by month and year. [1]Rate is equivalent to one or more SSTI cases per 100 training cycles. One training cycle consists of 105 days. Light grey bars represent MRSA SSTI cases while the dark grey line represents the MRSA-confirmed SSTI rates. NOTE: X and Y axis different from figure 3.5.

Skin and soft-tissue infections were classified into specific types of infection based on the associated ICD-9-CM code. Upon evaluation, it is apparent that diagnoses for cellulitis and/or abscess (ICD-9-CM codes (681-681.11 and 682-682.9) and "folliculitis" (704.8) compose the majority (80.8%) of SSTIs identified in this population (**Table 10a**). Diagnosis codes were further categorized as purulent and non-purulent infections which were described early within the methods section. Encounters for purulent infections further evaluated by cases associated with *S.aureus* and MRSA are shown in **figures 17a.** Approximately 27.0% of the purulent SSTI cases had an associated culture. Of those cultures, 87.6% were clinically confirmed positive for *S.aureus.* Over two-thirds of the clinically confirmed *S.aureus* related to purulent SSTI

(69.1%) met the case definition for MRSA. In contrast, only 2,273 (19.1%) of the non-purulent cases had a clinical culture obtained, of which 1,189 (83.1%) were positive for *S.aureus* and only 1,128 (49.6%) met the case definition for MRSA (**Figure 17b**).

Annual trends among overall, *S.aureus* and MRSA-purulent and non-purulent SSTI were evaluated. Below, in **figure 21,** it indicates that the absolute numbers of purulent diagnoses and their corresponding rates peaked in 2008 and then decreased slightly in 2009. The opposite trend was observed with respect to overall non-purulent cases and rates-they peaked in 2009 showing a steady increase from 2007 through 2009 (69 to 91infection per 100 TC) (**figure 22**). *S.aureus* and MRSA-non purulent cases and rates remained consistent with what was observed with their respective purulent counterparts-peaking in 2008 and declining thereafter.

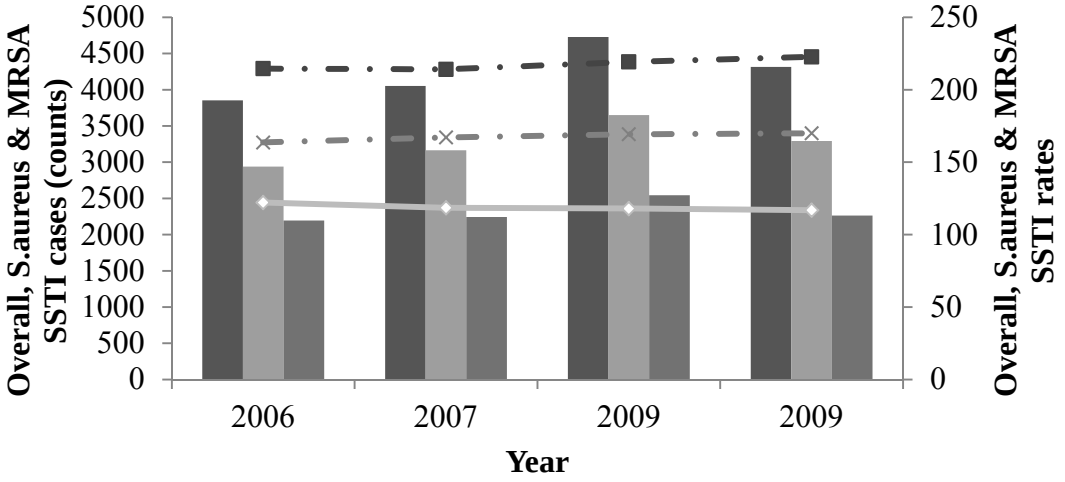


Figure 21 Annual overall, S.aureus and MRSA purulent SSTI case counts and rates. Dark gray bars depict overall purulent cases", light grey bars depicts S.aureus cases", and medium grey bars represent MRSA purulent SSTI. Dark grey dashed lines (squares) represent overall purulent rates; light grey (crosses) dashed lines represent S.aureus rates; and medium grey (diamonds) solid lines represent rates of purulent MRSASSTI. Rate is calculated as one or more infections per 100 training-cycles. One TC equals 105 days.

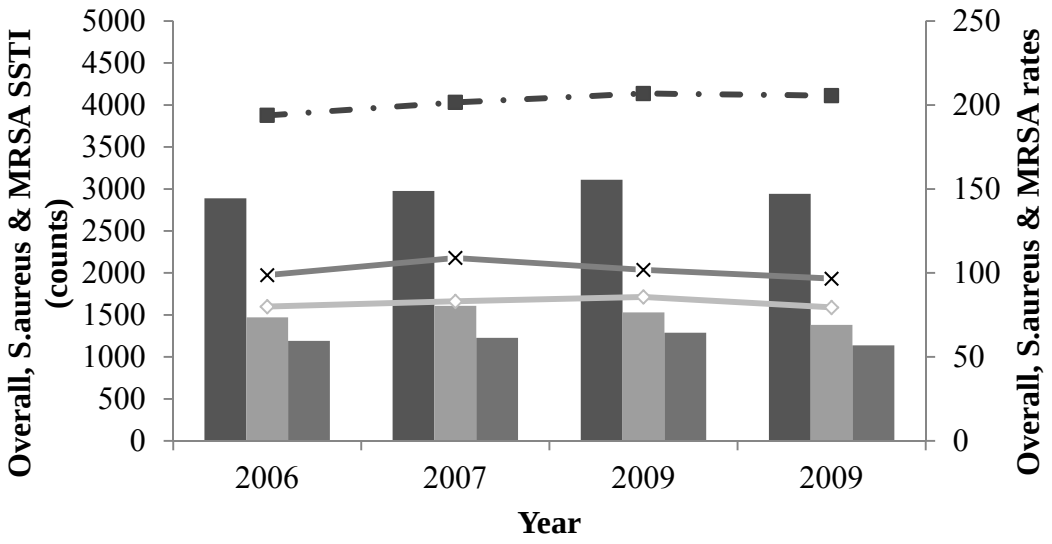


Figure 22 Annual overall, S.aureus and MRSA-confirmed non-purulent case counts and rates. Dark gray bars depict overall non-purulent cases; light grey bars depict *S.aureus* cases; and medium grey bars represent MRSA cases. Dark grey dashed lines represent overall non-purulent SSTI rates; light grey dashed lines represent *S.aureus* rates; and medium grey solid lines represent rates of MRSA non-purulent SSTI. Rate is calculated as one or more infections per 100 training-cycles. One TC equals 105 days.

Overall, *S.aureus* and MRSA SSTI followed similar trends with respect to the season in which the infection occurred. Analyses showed that the highest proportion of cases occurred during the summer months from July through September (**figure 23**). When overall, *S.aureus* and MRSASSTI rates were evaluated this trend changed. For overall SSTI, *S.aureus* and MRSA SSTI rates remained slightly higher in winter months (246, 162, and 109 infections per 100 TC) when compared to summer months (223,152,101 infections per 100 TC ($p<0.001$)). Conversely, when seasons were combined, all rate types for Spring/Summer months were only slightly higher than fall/winter months (**table 10b**).

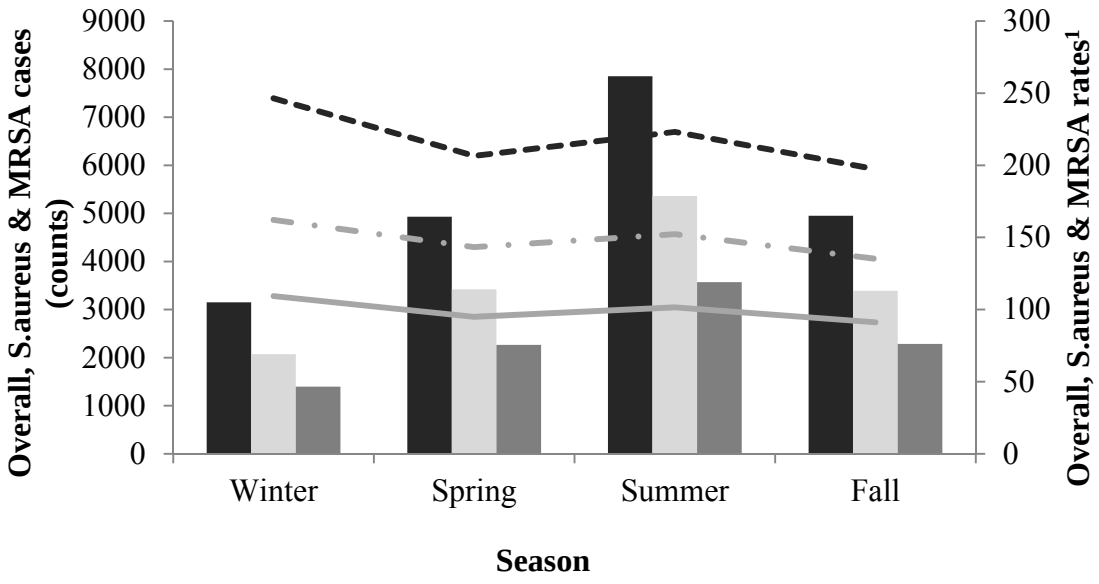


Figure 23 Seasonal overall, S.aureus and MRSA SSTI cases and rates. [1]Rates are calculated as one or more infections per 100 training-cycles. One training cycle is equivalent to 105 days. Dark gray bars depict overall SSTI cases"; light grey bars depicts S.aureus-confirmed cases"; and medium grey bars represent MRSA SSTI. Dark grey dashed lines represent overall SSTI rates, light grey dashed lines represent S.aureus-confirmed" rates; and medium grey solid lines represent rates of MRSA SSTI.

Phase of training

Overall, *S.aureus* and MRSA SSTI were also evaluated by phase of training. One Stop Unit Training is 14 weeks total, but it consists of two phases. Phase 1, basic combat training (BCT) lasts for 9 weeks, while phase 2-advanced individual training (AIT) - lasts for 5 weeks. Overall SSTI rates for phase 1 were twice the rates of phase 2 with 334.3 cases per 100 TC during phase 1 compared to 121.6 cases per 100 TC during phase 2. *S.aureus* and MRSA-confirmed SSTI followed a similar trend with 227 and 151 cases per 100 TC in phase 1 and 86 and 58 cases per 100 training cycles in phase 2 (over 2 times the rate. Statistical tests showed significant differences exist for overall, *S.aureus* and MRSA SSTI rates by training phase ($p<0.001$).

Phase of training by season

The figure below shows the incident cases and rates of overall, *S.aureus* and MRSA SSTI by phase of training and season. Most absolute numbers of cases of both overall, *S.aureus* and MRSA SSTI occurred during the summer months during phase 1. Rates of overall, *S.aureus* MRSA SSTI tended to be on average 3 times higher during phase one as compared to phase two during all seasons ($p<0.001$). Peak rates of overall and *S.aureus* SSTI occurred during phase 1 in the winter months; while peak MRSA SSTI rates occurred during phase 1 in the spring season. Base rates occurred during phase 2 of training in the winter months for overall, *S.aureus* and MRSA SSTI. (**Figure 24**)

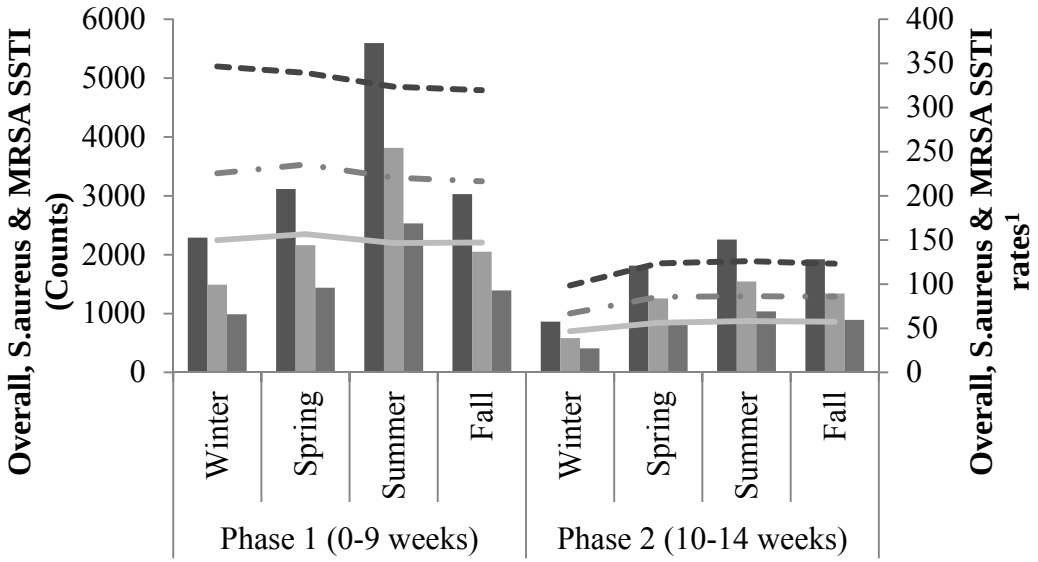


Figure 24 Incident cases and rates of overall, *S.aureus* and MRSA SSTI by phase of training and season.[1]Rates are calculated as one or more infections per 100 training-cycles. One training cycle is equivalent to 105 days. Dark gray bars depict overall SSTI cases; light grey bars depict S.aureus cases; and medium grey bars represent MRSA SSTI. Dark grey dashed lines represent overall SSTI rates, light grey dashed lines represent *S.aureus*- rates; and medium grey solid lines represent rates of MRSA SSTI ($p<0.001$).

Initial clinical care

Among those with an overall SSTI, 4,173 (20.0%) had an incision and drainage (I&D) procedure (**Table 11**). Trainees with a "cellulitis and abscess" diagnosis code (31.7%) were more likely than those without such a code (5.2%) to have an associated I&D procedure ($p<0.001$). Most SSTIs overall resolved, but 4% resulted in a complication (Table 3.2a)-rates of complication compared to resolution were slightly higher among *S.aureus* (5%) and MRSA SSTI (5%) cases ($p<0.001$).

Outpatient management was assessed by evaluating, the appointment type and disposition status. Overall SSTI had an acute appointment type (86.0%) and were released without limitations (66.6%). Trainees with a MRSA SSTI were more likely to be released with work limitations, assigned to quarters for convalescence and be admitted to the hospital compared to trainees with SSTI overall and *S.aureus* SSTI (**Table 11**). Inpatient management was also assessed using disposition status codes. Analyses showed that the average length of stay for overall SSTI inpatient visit was 5.73 days and 10.1 days for a MRSA SSTI (**Table 12**).

Incident skin and soft tissue infection cases (17,563, 84%) were linked with pharmacy data to evaluate the types of antibiotic regimens prescribed for such infections as well as the management of not only SSTI overall but also *S.aureus and* MRSA SSTI. Cases could have been prescribed more than one antibiotic per infection. The most commonly prescribed antibiotic for SSTI infections was trimethoprim-sulfamethoxazole (TMP-SMX) (n=8,879 [42.5%]). Doxycycline (4,426 [21.2 %]) and clindamycin (3,876 [18.6 %]) followed close behind. Other prescribed regimens included cephlasporins (14.8%), bactroban (13.5%), hydrocortisone (12.3%), and bacitracin (15.8%). Antibiotic coverage for MRSA SSTI was also assessed. MRSA coverage included TMP-SMX,

doxycycline, tetracycline, minocycline and clindamycin. Over 85% (13,099) of those trainees receiving an antibiotic for treatment were prescribed an antibiotic appropriate for MRSA SSTI (**Table 11**).

Lost time in training

Lost time in training (LTT) burden was calculated and analyzed by all demographic, disease outcomes, and disposition variables (**Tables 13, 15a-15d, 16**). A median of 2.00 days (IQR: 3.00, range: 0.50-102.5) was lost for overall SSTI cases. A total of 72,682 training days were lost during the entire study period. *S.aureus* and MRSA- confirmed SSTI cases lost almost twice as many days during training with each having a median of 3.5 days (IQR:5.00 days, range: 0.50-88 days) . When evaluated with combined confirmed and probable estimates for *S.aureus* and MRSA, the mean and median days lost were only slightly more than for overall SSTI. **Figure 25** below shows the mean lost time in training for overall, *S.aureus* and MRSA SSTI by month of training. Mean lost-time in training consistently remained higher for *S.aureus* and MRSA SSTI when compared with overall SSTI. Additionally, the number of days lost in training peaked in September (across all years of the study period (2006-2009)).

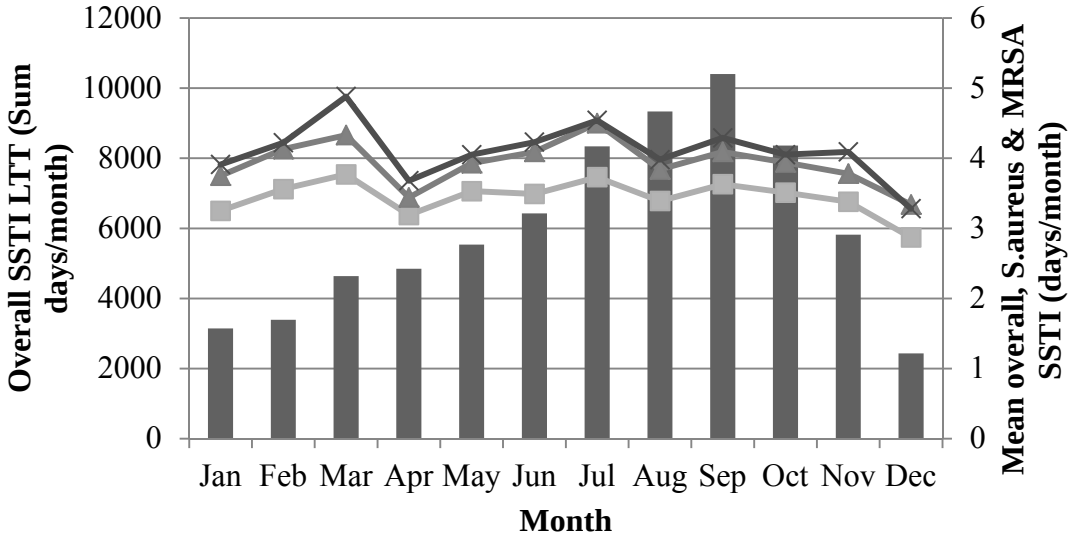


Figure 25 Overall, S.aureus and MRSASSTI mean and total lost time in training (LTT) by month. Bars represent total overall SSTI LTT days. Light (squares), medium (triangles), and dark (x) grey lines represent overall, *S.aureus* and MRSASSTI (respectively).

As mentioned previously, multiple factors contribute to the overall LTT estimate- lost time in the clinic, hospital, and ER visits; an assignment to quarters and/or limited duty; and being recycle. Approximately 20,800 individuals visited an outpatient clinic for an SSTI. The time spent during this visit was a median of 0.87 days (**Table 15a**).

A total of 354 (1.69 %) individuals with an SSTI were recycled from training. One-quarter of the time lost in training was due to being recycled (18,266 days (25.1%)). Median time for a recycle was 50 days (IQR: 4.0, range 48-97 days) A sensitivity analysis was performed to evaluate this specific population being recycled at different time intervals (0, 14, and 21 days of remedial training after a recycle) (**Table 15b**). This sub-population is similar to the overall SSTI population. The total number of days lost in training due to recycle was approximately 13,000, 18,000, and 20,000 days at 0, 14 and 21 days, respectively. This changed the total number of days lost at each time interval with the range being between 67,000 and 75,000 days. Being recycled from training contributes to one-quarter of the lost time in training burden at 14 and 21 days lost; while at 0 days remedial training, being recycled falls third behind work duty limitations and clinical visits.

There were a total of 10,519 instances in which persons were released with work duty limitations with a median disposition of 1.50 days (IQR: 1.5, range 1.5-21 days). Work limitations contributed one-third of the duty days lost (23,226 days). The remainder of the lost time in training consisted of days lost from clinical visits (18,017 days) and 'sick in quarters' disposition (11,760 days).

Overall, *S.aureus* and MRSA SSTI LTT was evaluated by phase and season of training (**Figure 26**). On average, MRSA SSTI LTT burden consistently remained higher

than overall SSTI burden, especially during the summer months in phase 1 of training ($p<0.001$). In fact, almost one- third of the training time lost for overall, *S.aureus,* and MRSA SSTI occurred during the summer months (21K, 17K, and 11K days, respectively). Overall SSTI LTT burden peaked in summer months during phase 1 but seemed to increase into the fall months during phase 2. Lost time in training burden evaluated for MRSA SSTI, on the other hand, showed peaks in the winter months during phase 1 and in the spring months for phase 2.

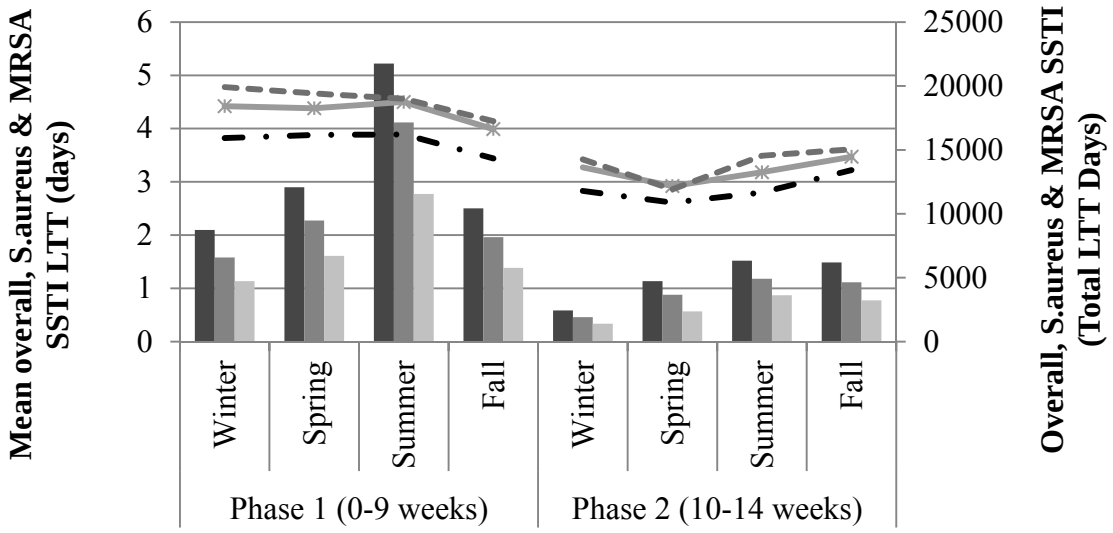


Figure 26 Mean and total lost time in training burden by training phase and season by overall, S.aureus and MRSA-Confirmed SSTI. Black (dash) line represents mean LTT for overall SSTI; light (x) and medium (dash) grey lines represent *S.aureus*- MRSA-confirmed SSTI mean LTT. Dark, medium and light grey bars represent MRSA, S.aureus, and Overall SSTI, respectively (p<0.001).

Univariate and multivariate analyses

Mann-Whitney U and Wilcoxon Rank Sum used to was used to evaluate certain parameter's effects on lost-time in training. Unadjusted means, 95% confidence intervals, and p-values were calculated for each parameter (**Tables 15a-15d**). Parameters were explored for those with an overall SSTI and specifically, recruit trainees with a *S.aureus* and MRSA SSTI. Initial univariate analysis showed sex, age, race, marital status, rank, training location military occupational specialty , phase of training, year of infection, purulent SSTI, complicated SSTI, culture for *S.aureus*, I&D procedure, and MRSA coverage were significantly associated with lost-time in training burden related to overall, *S.aureus* and MRSA SSTI (all p<0.001, respectively) (**Tables15a-15d**).

To identify potential significant differences in LTT of each value of the categorical factors, generalized linear modeling (GLM) with a negative binomial

distribution and log-link function was employed. Results showed that for those trainees with an SSTI overall, demographic factors significantly associated with greater lost time in training included older age (RR=1.11, p<0.001), married (RR=1.14, p<0.001), training location [Fort Jackson (RR=1.32, p<0.001); Fort Knox (RR=1.43, p<0.001); Fort Leonard Wood (RR=1.12, p<0.001); Fort Sill (RR=1.10, p<0.001)]. Additionally, with regards to clinical outcomes and management, purulent SSTI (R=1.16, p<0.001) clinical culture positive for MRSA (R=2.61, p<0.001), I&D(R=2.29, p<0.001), and complicated infections (RR=10.3, p<0.001) were all associated with an increased LTT. Three factors were significantly associated with a decrease in LTT- race (African American, RR=0.59; p<0.001), phase of training (phase 2, RR=0.78, p<0.001), and no MRSA coverage (RR=0.65, p<0.001).

The population was narrowed further to identify individual factors associated with LTT among those trainees with an *S.aureus* and MRSASSTI. Significant differences in LTT found among host-specific factors the overall SSTI group were also observed among those trainees with *S.aureus* and MRSA SSTI, specifically. The only difference being that sex (female) was significantly associated with an increase in LTT among trainees with *S.aureus* and MRSA SSTI (RR=1.14 and 1.24, p<0.001, respectively). Additionally, phase 2 of training was found to be significantly associated with a decrease in LTT compared to phase 1 among trainees with a *S.aureus* and MRSA SSTI (RR=0.75, p<0.001, respectively). This result is similar to what was found among the SSTI overall group. Similar methods were used to perform subsequent multivariate analyses. Those covariates with p-values less than 0.05 in the univariate analysis were considered for the multivariate models. Additionally, the variables must be mutually exclusive of one

another (not correlated). Variables were input using a backward method. Three models were created to explore the effect of host-specific, temporal, and clinical outcomes in addition to initial clinical care on lost time in training. The first model was a general overall model that included all recruits with an SSTI. The second and third models were *S.aureus* and MRSA SSTI specific.

Analyses revealed a final overall SSTI model that showed complicated SSTI (RR=7.96, p<0.001), , clinical culture positive for MRSA (RR=1.84, p<0.001), I&D procedure (RR=1.30, p<0.001), training location [Fort Jackson, SC (RR=1.39, p<0.001),Fort Knox, KY (RR=1.15, p<0.001), Fort Leonard Wood, MO (RR=1.07, p<0.002) and Fort Sill, OK (RR=1.09, p<0.001)], older age (RR=1.11, p<0.001) were related to a significant increase in LTT. On the other hand, no MRSA coverage (RR=0.79, p<0.001), training phase 2 (RR=0.77, p<0.001), year of infection beyond 2006 [2007, RR=0.96, p<0.001; 2008, RR=0.86, p<0.001; and 2009, R=0.96, p=0.049), season (fall/winter, RR=0.96, p<0.001), and race (African American, RR=0.87, p<0.001)) were related to reduced LTT.

For the full *S.aureus* and MRSA models (confirmed and probable cases included), similar results were found with respect to most variables listed in the overall SSTI model (**table 16**). Microbiology, antibiotic coverage and procedure type were removed from both the *S.aureus* and MRSA SSTI specific models because these variables were used to define potential probable cases; therefore, they are not mutually exclusive. Complicated cases (across all SSTI categories) experienced 7-8 times the increase in lost time in training compared to those individuals whose infection resolved (p<0.001) (**table 16**). Rate ratios were similar with respect to season, but confidence intervals were slightly

wider (likely reflecting the deduction in population size). Additionally, rate ratios among the training sites were slightly lower in the *S.aureus* and MRSA SSTI specific models compared with the overall SSTI, but the confidence intervals were slightly wider. Those within the "African American" race category, experienced much lower RR and slightly tighter 95% CI in the *S.aureus* and MRSA SSTI models compared with the overall SSTI model [RR=0.69 (0.66,0.71; RR=0.67 (0.65,0.70); and RR=0.87 (0.84,0.90), respectively]. (**Table 16**)

Full *S.aureus* and MRSA SSTI specific models were compared with their confirmed counterparts. Results showed similarities between the two models with respect to the covariates that were related to LTT. They included complication, phase of training, year of event, training location, and race variables. The *S.aureus* confirmed model was an improvement over the full *S.aureus* model when evaluating the goodness of fit measures. The deviance ratio moved closer to one (0.87 vs 0.97, respectively) and scatterplots revealed that most responses fell with ±2 standard deviations, which is another sign of a good fitting model. When evaluating the parameter estimates, results showed that for some variables, RR estimates had decreased but also had wider 95%CI (data not shown).

Improvements in model fit were not observed with respect to the MRSA-confirmed SSTI model compared with the full MRSA SSTI model. Goodness of fit measures decreased. The deviance ratio in the full MRSA SSTI model was 0.90 while it was 0.55 in the MRSA-confirmed SSTI model. Scatterplots also revealed that responses were tighter and within ±2 standard deviations with respect to full MRSA SSTI model compared with the confirmed MRSA SSTI model (data not shown).

Table 8 Overall, *S.aureus* and MRSA SSTI Case Demographic Characteristics [1,2]

Factor		**Overall SSTI** (N=20,884)		***S.aureus*- SSTI** (N=14,243)		**MRSA- SSTI** (N=9,522)	
	Person-days[3]	**Count (%)**	**Rate[4]**	**Count (%)**	**Rate[4]**	**Count (%)**	**Rate[4]**
Sex							
Male	887,300	18,187 (87.1)	215.2	12522 (88)	148	8366 (88)	99
Female	130,457	2,697 (12.9)	217.1	1721 (12)	139[5]	1156 (12)	93[5]
Race							
White	744,327	14,235 (68.2)	200.8[5]	9778 (69)	138	6450 (68)	91
Black	233,819	5,875 (28.1)	263.8	3934 (28)	177 [5]	2744 (29)	**123[6]**
Other	39,660	773 (3.7)	204.7	531 (4)	141	328 (3)	87
Age Category							
17-24	860,217	17,549 (84.0)	214.2	11945 (85)	146	7975 (85)	97
25-34	139,947	2,961 (14.2)	222.2	2034 (15)	153	1380 (15)	103[5]
Marital Status							
Single	830,273	16,943 (82.7)	214.3	11535 (83)	146	7699 (82)	97
Married	168,189	3,537 (17.3)	220.8	2440 (17)	152	1634 (18)	102
Education Level							
HS Diploma	649,425	13,398 (69.7)	216.6	9141 (70)	148	6114 (70)	99
Equivalency test	209,718	4269 (22.2)	213.7	2915 (22)	146	1941 (22)	97
Bachelor's degree	44,916	927 (4.8)	216.7	620 (5)	145	444 (5)	104
Completed one semester of college	31,273	625 (3.3)	209.8	416 (3)	140	276 (3)	93

[1]Demographic variables were obtained from the Defense Manpower Data Center (DMDC) and then merged with the M2 SSTI Medical Encounter data file. The information provided in this table is based on a service-member's first record in the file with an event that occurred during training (the event must have occurred within 105 days from the date of entry). Total trainee population was 254,027.[2]Tests for significance differences ($\alpha<0.05$) among rates with respect to demographic variables among those trainees with an infection during training and those without an infection during training were calculated using chi-square tests and Poisson regression. Reference value is the first value in each category.[3]Max amount of person-time is 105 days. Person-time for an event was calculated as the difference between the date of event (or departure) and the date of entry into training. Total person-time for MRSA SSTI was 136,087 days (not shown in table).[4]Rate is calculated as one or more infections per 100 training cycles (TC). One TC is equivalent to 105 days.[5]p-value$\leq$0.05.[6]p-value$\leq$0.001

Table 9 Overall, *S.aureus* and MRSA SSTI case characteristics [1,2]

Factor		**Overall SSTI** (N=20,884)		***S.aureus*- SSTI** (N=14,243)		**MRSA- SSTI** (N=9,522)	
	Person-days[3]	**Count (%)**	**Rate[4]**	**Count (%)**	**Rate[4]**	**Count (%)**	**Rate[4]**
Installation							
Ft Benning, GA	310,141	6,134 (29.4) [3]	207.7[6]	4261 (30)	144	2887 (30)	98
Ft Jackson, SC	323,578	6,617 (31.7)	214.7	4484 (31)	202	2970 (31)	134
Ft Knox, KY	102,499	2,055 (9.8)	210.5	1361 (10)	139	879 (9)	90[6]
Ft Leo. Wood, MO	171,784	3,621 (17.3)	221.3	2456 (17)	150	1656 (17)	101
Ft Sill, OK	109,845	2,457 (11.8)	234.9	1681 (12)	161[6]	1130 (12)	108[7]
Grade/Rank							
E1	456,768	9,446 (45.2)	217.1	6427 (45)	148	4288 (45)	99
E2	310,195	6,282 (30.1)	212.6	4296 (30)	145	2861 (30)	97
E3	197,147	4,045 (19.4)	215.4	2779 (20)	148	1840 (19)	98
E4	53,683	1,110 (5.3)	217.1	740 (5)	137	533 (6)	99
MOS							
Infantry	225,015	4,130 (19.8) [3]	192.7	2888 (20)	135	1966 (21)	92
Logistics	125,034	1,343 (6.4)	112.8	1818 (13)	153[6]	1178 (12)	99[6]
Medical	61,719	866 (4.1)	147.3	891 (6)	152[6]	612 (6)	104[7]
Communications	67,393	2,664 (12.8)	415.1	1103 (8)	172[6]	724 (8)	113[8]
Artillery	85,807	1,176 (5.6)	143.9	1204 (8)	147[6]	791 (8)	97
Armor	46,411	1,630 (7.8)	368.8	564 (4)	126[6]	338 (4)	76[7]
Other[5]	406,468	7,706 (36.9)	199.1	5775(41)	150	3943 (41)	102

[1]Demographic variables were obtained from the Defense Manpower Data Center (DMDC) and then merged with the M2 SSTI Medical Encounter data file. The information provided in this table is based on a service-member's first record in the file with an event that occurred during training (the event must have occurred within 105 days from the date of entry). Total trainee population was 254,027.[2]Tests for significance differences ($\alpha<0.05$) among rates with respect to demographic variables among those trainees with an infection during training and those without an infection during training were calculated using chi-square tests and Poisson regression. Reference value is the first value in each category.[3]Max amount of person-time is 105 days. Person-time for an event was calculated as the difference between the date of event (or departure) and the date of entry into training. Total person-time for MRSA SSTI was 136,087 days (not shown in table).[4]Rate is calculated as one or more infections per 100 training cycles (TC). One TC is equivalent to 105 days.[5] Other incudes multiple categories with small values such as aviation, mechanical maintenance, signal operations, etc. [6]P-value<0.05[7]P-value<0.01[8]P-value<0.001

Table 10a Overall SSTI, *S.*aureus and MRSA SSTI Disease Outcomes [1]

Factor		**Overall SSTI** (N=20,884)		***S.aureus*- SSTI** (N=14,243)		**MRSA- SSTI** (N=9,522)	
	Person-days[2]	**Count (%)**	**Rate[3]**	**Count (%)**	**Rate**	**Count (%)**	**Rate**
No. Unique Episodes per individual							
1	-	15,789 (75.6)	-	12751 (90)	-	8428 (89)	-
2	-	3,665 (17.5)	-	985 (7)	-	716 (8)	-
3	-	1,026 (4.9)	-	334 (2)	-	247 (3)	-
4 or more	-	404 (1.9)	-	173 (1)	-	131(1)	-
Type of SSTI dx							
Cellulitis and/or abscess	603,859	11,638 (48)	202.4	8856 (62)	154	5977 (63)	104
Carbuncle & furuncle	142,071	2,880(14)	212.9	2375 (17)	176	1740 (18)	130
Folliculitis	285,242	6,924 (33)	254.9	4731 (33)	174	3420 ()	126
Purulent SSTI	817,276	16,948	218	13,044(62)	168	9245 (66)	119
Non-Purulent SSTI	619,736	11,918	202	7882 (38)	134	4843 (34)	82
Complicated	43,213	857 (4.1)	208	670(5)	163	465 (5)	113[6]
Resolved	974,634	20,007 (95.4)	215	13,573	146	9057 (95)	98
Organism type							
S.aureus-confirmed	1,017,847	4154 (20)	42	4,154 (19)	42	4,154 (19)	42
MRSA[5]-confirmed	1,017,847	2,819 (67.0)	28	2,819 (67.0)	28.0	2,819 (67.0)	28.0
MSSA-confirmed	1,017,847	1,350 (31.0)	13	1,350 (31.0)	13.3	1,350 (31.0)	13.3
S.aureus-probable	1,017,847	10089 (48)	104	10,089 (48)	104	10089 (48)	104
MRSA-probable	1,017,847	6703 (66)	69	6703 (66)	69	6703 (66)	69
MSSA-probable	1,017,847	3386 (34	35	3386 (34	35	3386 (34	35

[1]The information provided in this table is based on a service-member's first record in the file with an event that occurred during training (the event must have occurred within 105 days from the date of entry). Total trainee population was 254,027.
[2]Max amount of person-time for an individual trainee is 105 days. Person-time for an event was calculated as the difference between the date of event (or departure) and the date of entry into training. Total person-time for MRSA SSTI was 136,087 days (not shown in table).[3]Rate is calculated as one or more infections per 100 training cycles (TC). One TC is equivalent to 105 days.
[4] A complication or severe infection is defined as having a diagnosis code for one of the following: erysipelas, necrotizing fasciitis, acute endocarditis, acute osteomyelitis, septicemia (MRSA or MSSA), pneumonia (*Staphylococcus),* and meningitis (*Staphylococcus).* Additionally, if an individual was hospitalized or assigned to remedial training, the case was deemed to be complicated.
[5] *Staphylococcus aureus* and Methicillin-resistant *Staphylococcus aureus*-confirmed cases have a culture positive for *S. aureus* as well as confirmatory resistance to oxacillin.[6]Tests for significance differences ($\alpha<0.05$) among rates with respect to demographic variables among those trainees with an infection during training and those without an infection during training were calculated using chi-square tests and Poisson regression. Reference value is the first value in each category; P-value<0.01.

Table 10b Overall, *S.aureus* and MRSA SSTI temporal factors

Factor		**Overall SSTI** (N=20,884)		***S.aureus*- SSTI** (N=14,243)		**MRSA- SSTI** (N=9,522)	
	Person-days[3]	**Count (%)**	Rate[4]	**Count (%)**	Rate[4]	**Count (%)**	Rate[4]
Season[2]							
Spring/summer	620,128	12,782 (61)	216	8,778 (62)	149	5837 (61)	99
Fall/winter	397,719	8,102 (39)	214	5,465(38)	144	3685 (39)	97
Year							
2006	240,246	4,837 (23.2)	211.4[6,7]	3254 (23)	142	2272 (24)	99
2007	246,524	4,997 (23.9)	212.8	3457 (24)	147 [6,7]	2308 (24)	98
2008	274,719	5,707 (27.3)	218.1	3951 (28)	151	2599(27)	99
2009	283,358	5343 (24.3)	198.0	3581 (25)	132	2343(25)	87
Phase of Training[5]							
Phase 1	440,603	14,028 (67.2)	334.3[6,7]	9518 (67)	227	6354 (67)	151
Phase 2	577,244	6,687 (32.0)	121.6	4725 (33)	86[6,7]	3168(33)	58[6,7]
Time to SSTI Event Follow-up Days for SSTI per infection (mean ± SD days)	-	48.7±29.5 range: 1-105		49.0±29.4 range: 1-105		49.0±29.4 range: 1-105	
	-	7.31±14.9 range: 1-100		5.17±11.3 range:1-98		5.15±11.2 range:1-98	

[1] The information provided in this table is based on the service-members first record in the file with an event that occurred during training (the event must have occurred within 105 days from the date of entry). Total trainee population was 254,027.
[2] Season defined as winter, spring, summer, and fall.[3]Max amount of person-time for an individual trainee is 105 days. Person-time for an event was calculated as the difference between the date of event (or departure) and the date of entry into training. Total person-time for MRSA SSTI was 136,087 days (not shown in table).[4]Rate is calculated as one or more infections per 100 training-cycles (TC). One TC is equivalent to 105 days. [5] One Stop Unit Training lasts for 14 weeks and is divided into two phases. The first phase of basic combat training lasts 9 weeks and the second (advanced individual training) lasts 5 weeks.[6]Tests for significance differences ($\alpha<0.05$) among rates with respect to demographic variables among those trainees with an infection during training and those without an infection during training were calculated using chi-square tests and Poisson regression. Reference value is the first value in each category.
[7]P-value<0.05

Table 11 Overall, *S.aureus* and MRSA- SSTI initial outpatient medical care [1]

Factor	n	**Overall SSTI** (N=20,884) **Count (%)**	***S.aureus*- SSTI** (N=14,243) **Count (%)**	**MRSA- SSTI** (N=9,522) **Count (%)**
Outpatient Appointment Type	20,884			
Acute		17,965 (86.0)	12534 (60)	8481 (41) [3,4]
ER		2,768 (13.3)	2087 (10) [3,4]	1556 (7) [3,4]
Follow-up		4,298 (20.6)	3253 (16) [3,4]	2226 (11)
Routine		1,759 (8.4)	1334 (6)	885 (0.04) [3,4]
Disposition	20,884			
Released w/o limits		13,914 (66.6)	9620 (46)	6514 (68) [3,4]
Released w limits		11,306 (54.1)	8345 (40)	5739 (60) [3,4]
Sick in quarters		3,001 (14.4)	2363 (11) [3,4]	1607 (17) [3,4]
Admitted		571 (2.7)	464 (2)	321 (3) [3,4]
Patient type				
Outpatient	1,017,078	20,868 (100)	14236 (100)	9521 (67)
Inpatient	42,322	845 (4) [3,4]	662 (5) [3,4]	461 (3) [3,4]
Procedures	18,398			
Incision & drainage[2]		4,173 (20.0)	3,848 (27) [3,4]	2845 (30)[3,4]
Antibiotic Regimen	17,563			
MRSA coverage		13,099 (85)	10,108 (90) [3,4]	6969 (92) [3,4]
Non-MRSA coverage		2,360 (15)	1132 (10)	602(8)

[1] The information provided in this table is based on the service-members first record in the file with an event that occurred during training (the event must have occurred within 105 days from the date of entry). Total trainee population was 254,027.[2] Incision and drainage was defined by procedure codes 10060, 10061, 10080, and 10081 (incision and drainage of abscess and incision and drainage of pilonidal cyst, respectfully).

Table 12 Overall, *S.aureus* or MRSA-SSTI inpatient medical care

Factor	Overall SSTI (N=20,884)[1]		*S.aureus*- SSTI (N=14,243)[2]		MRSA- SSTI (N=9,522)[2]	
	n	**Count (%)**	**n**	**Count (%)**	**n**	**Count (%)**
Inpatient Encounter Type	845		662		461	
Length of Stay mean ± SD days, range, sum		5.73 ± 6.61, range:1-63, 4839 days		6.58±8.87, range:1-63, 3625 days		10.1 ±10.1,range:1-39, 2625 days

[1] The information provided is based on the service-members first record in the file with an event that occurred during training (the event must have occurred within 105 days from the date of entry). Total trainee population was 254,027.[2]Total N is the sum of confirmed and probable *S.aureus* and MRSA SSTI, respectively.

Table 13 Total days of lost-time in training for incident SSTI encounters

	Total lost time in training						
	Total	**Clinic**	**ER**	**Hospital**	**Sick in quarters**	**Work duty limitations**	**Recycle**
N	20884	20802	588	381	2644	10519	354
Mean	3.4802	.8661	.9260	2.2782	4.4478	2.2080	51.5989
Std. Deviation	7.94124	.98853	1.58385	.85611	2.89557	1.48116	5.96568
Median	2.0000	.5000	.5000	2.0000	3.0000	1.5000	50.0000
IQR	3.0000	0.0000	0.5000	1.0000	3.0000	1.5000	4.0000
Mode	.50	.50	.50	3.00	3.00	1.50	48.00
Minimum	.50	.50	.50	1.00	3.00	1.50	48.00
Maximum	102.50	19.00	31.50	6.00	33.00	21.00	97.00
Sum	**72,682**	**18,017**	**545**	**868**	**11,760**	**23,226**	**18,266**

[1]All time measures reported in days; all measures reported (mean and median) are unadjusted; Interquartile range (IQR)

Table 14 Sensitivity analysis of days lost in training from recycling 0, 14, and 21 days of remedial training

	Recycle (Lost time in Training)			Total Lost time in Training		
	0	**14**	**21**	**0**	**14**	**21**
N	354	354	354	20884	20884	20884
Mean	37.5989	51.5989	58.5989	3.2429	3.4802	3.5989
Std. Deviation	5.96568	5.96568	5.96568	6.33950	7.94124	8.77212
Median	36.0000	50.0000	57.0000	2.0000	2.0000	2.0000
IQR	4.0000	4.0000	4.0000	3.0000	3.0000	3.0000
Mode	34.00	48.00	55.00	.50	.50	.50
Minimum	34.00	48.00	55.00	.50	.50	.50
Maximum	83.00	97.00	104.00	88.50	102.50	109.50
Sum	**13,310**	**18,266**	**20,744**	**67,726**	**72,682**	**75,160**

[1]All time measures reported in days; all measures reported (mean and median) are unadjusted; Standard deviation (SD); Interquartile range (IQR)

Table 15a Univariate analysis of lost time in training (LTT) burden among demographic factors[1]

Factor [2]	Overall SSTI LTT (days) **N=20,884**			*S.aureus*- LTT (days) **N=14,243**			MRSA LTT (days) **N=9,522**		
	n	Median (IQR)	p-value[3]	n	Median (IQR)	p-value[3]	n	Median (IQR)	p-value[3]
Sex									
Male	18,187	2.0 (3.0)	0.030	12522	2.0 (3.0)	0.320	8366	2. 0 (3.0)	0.010
Female	2697	2.0 (3.0)		1721	2.0 (3.5)		1156	2.0 (4.5)	
Age									
17-24	17,549	2.00 (3.00)	0.000	11945	2.0 (3.0)	0.030	7975	2.0 (3.0)	0.010
25-34	2961	2.00 (3.00)		2034	2.0 (3.0)		1380	2.0 (3.0)	
Race									
White	14,235	2.0 (3.0)	0.000	9778	2.0 (3.5)	0.000	6450	2.0 (4.0)	0.000
Black	5875	2.0 (1.5)		3934	2.0 (1.5)		2744	2.0 (1.5)	
Other	773	2.0 (3.0)		531	2.0 (4.5)		328	2.0 (4.9)	
Marital Status									
Single	16,943	2.00 (3.00)	0.000	11535	2.0 (3.0)	0.000	7699	2.0 (30)	0.000
Married	3537	2.00 (3.00)		2440	2.0 (3.5)		1634	2.0 (4.0)	
Education									
HS Diploma	13,398	2.00 (3.00)	0.385	9141	2.0 (3.0)	0.818	6114	2.0 (3.0)	0.030
Equivalency Test	4269	2.00 (3.00)		2915	(3.0)		1941	2.0 (3.0)	
Bachelor's degree	927	2.00 (3.00)		620	2.0 (3.0)		444	2.0 (3.0)	
One semester of College	625	2.00 (3.00)		416	2.0 (3.0)		276	2.0 (3.0)	

[1] Analyses were performed using non-parametric methods (Mann-Whitney U or Kruskal Wallace depending on the independent categorical variable).[2]Factors were evaluated for significance. Those factors with p-values <0.05 were included in subsequent multivariate analyses.[3]Considered significantly different at $\alpha<0.05$

Table 15b Univariate analysis of lost time in training burden among demographic factors[1]

	Overall SSTI LTT (days)			*S.aureus* LTT (days)			MRSA- LTT (days)		
Factor [2]		**N=20,884**			**N=14.243**			**N=9522**	
	n	Median (IQR)	p-value[3]	n	Median (IQR)	p-value[3]	n	Median (IQR)	p-value[3]
Rank									
E01	9446	2.00 (3.00)	0.039	6427	2.0 (3.0)	0.072	4288	2.0 (3.0)	0.589
E02	6282	2.00 (3.00)		4296	2.0 (3.0)		2861	2.0 (3.0)	
E03	4045	2.00 (3.00)		2779	2.0 (30)		1840	2.0 (30)	
E04	1110	2.00 (3.00)		740	2.0 (3.0)		533	2.0 (3.0)	
Location									
Fort Benning	6134	2.00 (2.00)	0.000	4261	2.0 (3.0)	0.000	2887	2.00 (3.0)	0.000
Fort Jackson	6617	2.00 (3.00)		4484	2.0 (3.5)		2970	2.0 (4.0)	
Fort Knox	2055	2.00 (3.00)		1361	2.0 (3.0)		879	2.0 (3.0)	
Fort Leonard Wood	3621	2.00 (2.00)		2456	2.0 (3.0)		1656	2.0 (3.0)	
Fort Sill	2457	2.00 (3.00)		1681	2. 0 (3.0)		1130	2.0 (3.0)	
MOS									
Infantry	4130	2.00 (2.50)	0.000	2888	2.0 (3.0)	0.000	1966	2.0 (3.0)	0.002
Logistics	2664	2.00 (3.00)		1818	2.0 (3.0)		1178	2.0 (3.5)	
Medical	1369	2.00 (2.00)		891	2.0 (3.0)		612	2.0 (3.0)	
Communications	1630	2.00 (2.00)		1103	2.0 (3.0)		724	2.0 (3.0)	
Artillery	1764	2.00 (3.00)		1204	2.0 (3.0)		791	2.0 (3.5)	
Armor	866	2.00 (3.00)		564	2.0 (3.5)		338	2.0 (4.0)	

[1] Analyses were performed using non-parametric methods (Mann-Whitney U or Kruskal Wallace depending on the independent categorical variable).[2]Factors were evaluated for significance. Those factors with p-values <0.05 were included in subsequent multivariate analyses.[3]Considered significantly different at $\alpha<0.05$

Table 15c Univariate analysis of lost time in training burden temporal and disease outcome factors[1]

Factor [2]	Overall SSTI LTT (days) N=20,884			*S.aureus* LTT (days) N=14,243			MRSA- LTT (days) N=9,522		
	n	Median (IQR)	p-value[3]	n	Median (IQR)	p-value[3]	n	Median (IQR)	p-value[3]
Training Phase									
Phase 1 (BCT)	14,030	2.00 (3.00)	0.000	9518	2.0 (3.5)	0.000	6354	2.0 (3.5)	0.000
Phase 2 (AIT)	6854	2.00 (2.00)		4725	2.0 (3.5)		3168	2.0 (3.0)	
Season									
Winter	3151	2.00 (3.00)	0.099	2074	2.0 (3.0)	0.02	1398	2.0 (3.0)	0.164
Spring	4930	2.00 (3.00)		3419	2.0 (3.0)		2266	2.0 (3.5)	
Summer	7852	2.00 (3.00)		5359	2.0 (3.5)		3571	2.0 (3.5)	
Fall	4951	2.00 (2.50)		3391	2.0 (3.0)		2287	2.0 (3.0)	
Year of infection									
2006	4837	2.00 (3.00)	0.000	3254	20 (3.5)	0.000	2272	2.0. (4.0)	0.000
2007	4997	2.00 (3.00)		3457	2.0 (3.5)		2308	2.0 (3.5)	
2008	5707	2.00 (2.50)		3951	2.0 (3.0)		2599	2.0 (3.0)	
2009	5343	2.00 (3.00)		3581	2.0 (3.0)		2343	2.0 (3.0)	
SSTI type									
Purulent	14,518	2.00 (3.50)	0.000	13,044	2.0 (3.0)	0.000	9245	2.0 (3.5)	0.000
Non-purulent	6366	1.00 (1.50)		7882	2.0 (3.5)	0.000	4843	2.0 (3.5)	0.000
Microbiology									
No culture	16,482	2.0 (1.5)	0.000	10509	2.0 (2.0)	0.000	6932	2.0 (2.0)	0.000
Culture Other	671	2.0 (3.0)		3	15				
Culture MRSA	2590	3.5 (5.5)		2590	3.5 (5.5)				
Culture MSSA	1141	2.5 (4.0)		1141	2.5 (4.0)		2590	3.5 (5.5)	

[1] Analyses were performed using non-parametric methods (Mann-Whitney U or Kruskal Wallace depending on the independent categorical variable).[2]Factors were evaluated for significance. Those factors with p-values <0.05 were included in subsequent multivariate analyses.[3]Considered significantly different at $\alpha<0.05$[4] 'Abscess cellulitis' includes ICD-9-CM codes such as 680-680.9 (carbuncle and/or furuncle) and 682-682.9 (cellulitis and or abscess). 'Non-abscess cellulitis' includes ICD-9-CM codes such as 684 (impetigo), 704.8 (folliculitis), 910.3 (infected blister).

Table 15d Univariate analysis of lost time in training burden and initial clinical care[1]

	Overall SSTI LTT (days)			*S.aureus* LTT (days)			MRSA-confirmed LTT (days)		
Factor [2]		**N=20,884**			**N=14,243**			**N=2819**	
	n	Median (IQR)	p-value[3]	n	Median (IQR)	p-value[3]	n	Median (IQR)	p-value[3]
Procedure									
Incision & drainage	4173	3.50 (4.50)	0.000	3848	3.5 (5.0)	0.000	2845	3.5 (5.0)	0.000
Disposition									
Work limits	17,965	2.00 (3.00)	0.000	8345	2.00 (3.0)		5739	2.5 (3.5)	
Quarters	4298	3.00 (5.00)	0.000	2363	(70)		1607	6.5 (7.0)	
Status									
Resolved	20,027	2.0 (2.0)		13573	2.0 (3.0)		9057	2.0 (3.0)	
Complicated	857	11.0 (50.5)	0.000	670	11.5 (50)	0.000	465	11 (51)	0.000
Antibiotic									
MRSA Coverage	13,099	2.00 (3.50)	0.000	10108	2.0 (4.0)	0.000	6969	2.0 (4.5)	0.000
No MRSA Coverage	2360	2.00 (1.50)		1132	2.0 (2.0)		602	2.0 (2.0)	

[1] Analyses were performed using non-parametric methods (Mann-Whitney U or Kruskal Wallace depending on the independent categorical variable). Means reported are unadjusted.[2] Factors were evaluated for significance. Those factors with p-values <0.05 were included in subsequent multivariate analyses.[3]Considered significantly different at $\alpha<0.05$[4]MRSA coverage includes TMP-SMX, Doxycycline, tetracycline, minocycline, and clindamycin antibiotic type prescriptions. Non-MRSA coverage includes cephalosporin, amoxicillin, and quinolone antibiotic type prescriptions.

Table 16 Factors associated with lost-time in training burden, final multivariate models[1,2]

		Overall SSTI Model					S.aureus SSTI Model					MRSA SSTI Model				
Factor		n	Mean	Rate ratio	95% CI	p-value	n	Mean	Rate ratio	95% CI	p-value	n	Mean	Rate ratio	95% CI	p-value
Clinical Outcomes																
Resolution	Complicate	742	25.1	7.96	7.6,8.4	0.000	645	25.1	8.7	8.27,9.25	0.00	448	25.5	8.3	7.78,8.92	0.00
	Resolve	14437	3.1	**Ref**			13334	2.9	**Ref**			8907	3.1	**Ref**		
Microbiology	No culture	11326	6.6	**Ref**												
	Other organism	521	7.7	1.12	1.1,1.2	0.000										
	MSSA	1006	10.0	1.51	1.4,1.6	0.000										
	MRSA	2326	12.2	1.84	1.8,1.9	0.000										
Initial care																
Antibiotic	MRSA coverage	12861	10.0	**Ref**												
	No coverage	2318	7.9	0.79	0.76,0.82	0.000										
Procedure type	I&D	3750	10.1	1.30	1.25,1.35	0.000										
	Other procedure	11429	7.8	**Ref**												
Temporal factors																
Training phase	Phase 1	9902	10.1	**Ref**			9332	9.7	**Ref**			6242	10.0	**Ref**		
	Phase 2	5277	7.8	0.77	0.75,0.80	0.000	4647	7.4	0.77	0.74,0.79	0.000	3113	7.8	0.78	0.75,0.81	0.000
Season	Fall/winter	5763	8.7	0.96	0.93,0.99	0.006	5347	8.3	0.96	0.93,0.99	0.004	3607	8.6	0.96	0.92,0.99	0.022
	Spring/summer	9416	9.1	**Ref**			8632	8.7	**Ref**			5748	9.0	**Ref**		
Year	2006	3679	9.5	**Ref**			3219	9.2	**Ref**			2246	9.8	**Ref**		
	2007	3819	9.2	0.96	0.93,1.00	0.049	3380	8.7	0.94	0.90,0.98	0.002	2261	9.1	0.93	0.89,0.98	0.007
	2008	4111	8.2	0.86	0.93,0.90	0.000	3872	7.9	0.85	0.82,0.89	0.000	2545	8.1	0.83	0.79,0.87	0.000
	2009	3570	8.7	0.92	0.88,0.95	0.000	3508	8.2	0.89	0.85,0.93	0.000	2303	8.4	0.86	0.82,0.91	0.000
Host-specific factors																
Training center	Fort Benning	4399	7.8	**Ref**			4203	7.5	**Ref**			2846	7.9	**Ref**		
	Fort Jackson	4771	10.9	1.39	1.34,1.44	0.000	4383	10.2	1.36	1.31,1.42	0.000	2910	10.5	1.33	1.27,1.40	0.000
	Fort Knox	1587	9.0	1.15	1.10,1.21	0.009	1341	8.3	1.11	1.05,1.17	0.000	866	8.9	1.13	1.05,1.20	0.001
	Fort Leonard	2665	8.4	1.07	1.02,1.11	0.002	2409	8.4	1.12	1.07,1.17	0.000	1626	8.7	1.10	1.04,1.16	0.001
	Fort Sill	1757	8.6	1.09	1.04,1.14	0.001	1643	8.2	1.10	1.04,1.16	0.000	1107	8.4	1.07	1.10,1.14	0.036
Race	White	11299	9.5	**Ref**			9602	9.7	**Ref**			6337	10.2	**Ref**		
	Black	3291	8.2	0.87	0.84,0.90	0.000	3870	6.6	0.69	0.66,0.71	0.000	2702	8.6	0.67	0.65,0.70	0.000
	Other	589	9.0	0.95	0.88,1.01	0.116	507	9.5	0.98	0.91,1.06	0.612	316	9.9	0.97	0.88,1.07	0.550
Age	17-24	13040	8.5	**Ref**			11945	8.1	**Ref**			7975	8.3	**Ref**		
	25-34	2139	9.4	1.11	1.07,1.15	0.000	2034	8.9	1.10	1.06,1.15	0.000	1380	9.3	1.12	1.06,1.17	0.000
Sex	Male						12297	8.2	**Ref**			8226	8.4	**Ref**		
	Female						1682	8.7	1.06	1.01,1.11	0.010	1129	9.3	1.11	1.05,1.18	0.000

[1]A generalized linear model with negative binomial distribution was used to evaluate a parameter's effect on the lost-time in training burden. Dependent Variable: Lost time in training (days)[2]Reference values are in bold (**Ref**). Shaded areas are those parameters that were not included in the final model.

Chapter 3: Estimation of the Economic Burden of *Staphylococcus aureus* skin and soft tissue among Army Recruit Trainees from 2006 through 2009 (Part II)

ABSTRACT

Background: Military trainees are known to be at risk for Staphylococcus aureus related skin and soft tissue infections. Little is known about the economic burden of this illness in this population in terms of direct medical and indirect costs.

Purpose: Calculate the direct medical and indirect costs of SSTIs and MRSA-associated SSTIs using a cost-of-illness framework.

Methods: Existing military health system datasets were used to conduct a retrospective, descriptive study, not involving human research, to assess the overall, S.aureus and MRSA-confirmed SSTI cost-of-illness (COI) among the Army active duty recruit trainee population visiting military treatment facilities for care at five Army Training Installations from 2006 to 2009. A hybrid COI study was employed to determine direct medical and indirect costs associated with such SSTIs. This cost analysis involved both established COI methods and novel cost modeling techniques.

Results: Total cost-of-illness (COI) for having an overall, S.aureus or MRSA-SSTI while in training were 51.5Million (M) United States Dollars (USD), 39.7M and 27.7M USD, respectively. Median COI per incident infection was 1230.51 (IQR: 1739.39), 1264.64 (IQR: 1971), and 1271.67 (IQR: 2089) USD for overall, S.aureus and MRSA SSTI. Total direct and indirect medical costs were 9.98M [median=139.76 (IQR: 210.95)] and 41.6M [median=1123.01 (IQR: 1671.53)] for SSTI overall. Hospital costs made up the majority of the direct medical costs, with sum costs being 5.19M [median=4867.57 (IQR: 5136.29] USD for SSTI overall. S.aureus and MRSA-SSTI contributed to a 70% and one-half of these costs (3.73M, USD and 2.66M, USD),

respectively. Indirect costs were substantial, comprising 80% of the total COI. Work duty limitation contributed to most of these costs (sum=13.3M USD (median=1262.43 9IQR: 842.16), with time lost to a recycle and clinical visit costs following close behind with 10.4M and 10.3 M, USD, respectively. The median cost per recycle was 28,786.26 USD (IQR: 2115.43) compared with 561.51USD (IQR: 829.27) for a clinic visit. Multivariate analysis showed that for overall SSTI, complicated SSTI, confirmed MRSA culture, incision and drainage procedure, training location, and age group (25-34) were all associated with an increase in total COI ($p<0.001$). Conversely, training phase (2), year of infection (2008), rank (E04), and race (African American) were all significantly associated with a decrease in total COI ($p<0.001$).

Conclusions: Using estimates of direct medical and indirect costs from this study, paired with incidence estimates from previous studies, we can use this information to expand on this knowledge and conduct more robust cost-effectiveness analyses in the future. From the analysis, it is apparent that having a S.aureus or MRSA SSTI relates to higher costs, both direct and indirect costs. Approximately 5% of those trainees experiencing an S.aureus- or MRSA SSTI had a hospitalization and contributed to between 50 and 70% of the costs associated with such visits. Hospitalization for long periods of time can lead to a recycle. In this population, only 1.7% of the trainees experienced a recycle, but 50% of them had been hospitalized at one point. Recycling a trainee comprised 25% of the total indirect costs behind work duty limitation disposition (32%). The impact of indirect costs is substantial, considering it made the most contribution to total COI. This information should be used to evaluate how to prevent an infection from getting to the point of hospitalization in which a trainee must recycle or

receive work duty limitations. These infections not only degrade force readiness they consume sparse resources that could be directed toward prevention of these infections. In an era of limited resources such as time, money, and personnel, more effort needs to be put into improving primary prevention of overall SSTI in order to limit the need to seek tertiary care and convalescence beyond such care in this population. The ultimate goal is to have a recruit trainee complete training from start to end without interruptions, but this can only be done if we prevent these infections from occurring in the first place.

INTRODUCTION

Background

The burden of skin and soft tissue infections (SSTIs) in terms of cost of illness is not well understood in the military training environment. Little is known about the burden of these infections on the military healthcare system.(8; 9; 28; 51) Disproportionately higher rates of overall and methicillin resistant *Staphylococcus aureus* (MRSA)-associated SSTIs among military training populations can result in an increased health care burden and impairment in the ability of soldiers to participate in and successfully complete training programs. Additionally, beyond the training setting, community acquired MRSA-associated SSTIs are frequently encountered in deployed soldiers. (165)

Previous studies

Costs associated with SSTI can be measured as direct medical costs (e.g. outpatient care, hospital care, laboratory procedures, prescription, etc.) and indirect costs (e.g. morbidity). Few studies have attempted to address costs of SSTIs or MRSA-associated SSTIs in the United States. Most importantly, no peer-reviewed evaluations exist regarding costs of SSTI or MRSA-associated SSTI in active duty military trainee populations. Five studies were identified in a literature search regarding this topic (**appendix A**).(58; 70; 111; 115; 129; 136) Of the studies that have explored the SSTI cost burden in the United States, most have focused on the inpatient population or complicated skin and skin structure infections (cSSSIs). Two studies estimated health-care costs in outpatient settings, of which only one determined cost of SSTI due to *Staphylococcus aureus (S.aureus).*(58; 129) Studies about the medical costs of MRSA

have been performed primarily in inpatient settings.(111; 136) Cost estimates varied with each study. Total costs calculated for MRSA-associated infections were as low as $4500 per case and as high as $35,000 per case. This wide cost range exemplifies the vast methodological differences (i.e., how costs were calculated as well as how illness was defined/evaluated).

With the sparse number of COI studies related to SSTI in the community setting, many uncertainties still remain, especially with regards to cost of SSTI and MRSA-associated SSTI in the active duty military population overall and, more specifically, the active duty military trainee population. A study of the cost of SSTI and MRSA-associated SSTI among active duty military trainees is important for a number of reasons. First, more comprehensive estimates of the burden of SSTIs and MRSA-associated SSTI on the military health care system are needed. Second, trainees are known to be at high-risk for SSTI and MRSA-associated SSTI. Understanding the costs associated with care and treatment of an active duty military trainee with SSTI can better direct allocation of resources (e.g. where patient should receive care or how patients should receive care). Moreover, there are indirect costs to SSTI (e.g. lost productivity): each lost recruit costs DoD approximately $35,000 to recruit, access, and train a replacement.(158) In the advent of new prevention measures to reduce SSTI and MRSA-associated SSTI in the trainee population, cost estimates generated from this study can serve as a baseline for comparison (i.e. treatment vs. prevention) for cost-effectiveness (CE) analysis. Ultimately, a detailed assessment of the costs of SSTI and MRSA-associated SSTI can influence both patient care and prevention policy.

The purpose of this study was to derive cost estimates of overall, *S.aureus* and MRSA SSTI in the active duty military trainee population. The primary objective was to determine the direct medical (ambulatory and hospital care) and indirect (lost work productivity) costs of SSTI and MRSA-associated SSTI among active duty Army trainees while in training using a cost of illness framework. In order to meet this objective, this study costs associated with SSTI and MRSA-associated SSTI by using existing military health system cost information. Additionally, this study measured the association between costs of SSTI and potential associations between clinical outcomes, initial clinical care, temporal and host specific factors through univariate and multivariate analyses.

METHODS

A cost-of-illness (COI) study was conducted to estimate the direct medical and indirect costs incurred from diagnoses of SSTI and MRSA-associated SSTI among the active duty military trainee population. This COI study was done from a military healthcare system perspective. All costs of medical resources used related to an initial SSTI (MRSA-associated SSTI) and subsequent follow-up visits from the initial diagnosis of SSTI within the 14-week training cycle were considered for inclusion in the study. The length of the training cycle for the purposes of this study was 98 (±) 5 days. Medical resources included personnel, treatment, and testing sources. Physicians, nurses and laboratory workers were considered personnel involved in the treatment and testing of patients. Treatment involved wound care or antimicrobial prescriptions. Testing included microbiologic tests of wound cultures for antibiotic susceptibility.

Study population

The study population was described in earlier reports (Chapter 3 Part I). Briefly, the population of interest was the active duty Army recruit trainee population. This population was defined as Army active component service members with a rank of E1 to E4 who served at one of the five Army One Stop Unit Training locations during an Army-specific training period following a first ever personnel record.(18)

Data sources

Existing de-identified military health data were used to assess the costs of SSTI and MRSA-associated SSTI among active duty military recruit trainees visiting military treatment facilities (MTFs) from 2006 through 2009. All data retrieval and analyses were performed from March 2012 through February 2014. This study was approved as

“Exempt” by the Uniformed Services University of the Health Sciences Infectious Disease Institutional Review Board on 10 February 2012 and approved by the Army Institute of Public Health.

Direct medical and indirect cost data (DMC and IDC, respectively) were provided from the previously described data sources. DMC variables were obtained from the Military Health System Mart (M2) databases. These databases included clinical, hospital, disposition and pharmaceutical data files. IDC estimates were also calculated using information from M2 and incorporated estimates from the Army Military-Civilian Cost System (AMCOS) Lite database to determine lost productivity.

M2 contains multiple cost variables. The primary cost variable used to calculate ambulatory and hospital cost was the “Variable Cost” variable. Variable costs are based on the prior fiscal year’s Medical Expenditures Reporting System (MEPRS). Additionally, variable costs are adjusted for inflation. Hospital, inpatient care, variable cost estimates were generated in a similar fashion except a completion factor is used to generate total full cost rather than a RVU.

The AMCOS database was used to determine the cost associated with being a trainee. This database contains a comprehensive file of personnel-related cost factors such as average basic pay rates and training costs across military occupational specialty (MOS) and pay-grade (E01-E04) as well as military procurement and operation and maintenance costs.(1)

Measured outcomes

In this analysis, costs were associated with three main categories: (1) clinical outpatient care; (2) hospital care; and (3) lost time in training. For the first two categories, epidemiological burden was measured by assessing the number of visits (initial and follow-up), monthly, annual, and seasonal rates of clinical or hospital incidence for SSTI and MRSA-associated SSTI and direct medical costs. Direct medical costs (DMC) were calculated as the sum of clinical outpatient, ER and hospital care costs. Assumptions and calculations for this variable can be found in **appendix G**.

Lost time in training (LTT) burden was assessed by using methods established by the Army Health Hazard Assessment Program's Medical Cost Avoidance Model.(1) Lost-time in training was calculated as the amount of time spent away (days) from training in order to receive care during a medical encounter (i.e., clinic, ER, or hospital visit) as well as being assigned to limited duty or 'sick in quarters' status, or being recycled from training. (1) Army regulations state that a recycle is "Any soldier who is delayed in the completion of training due to repeating certain phases of training. This includes personnel delayed for medical reasons…" (AR 612-201-24 February 2011).(21) Additionally, the trainee with an infection must have spent greater than three days in the hospital after being diagnosed with an SSTI. Using a conservative approach we estimated that lost-time for a recycle is equivalent to the sum of the length of stay in the hospital, 30 days convalescent leave, and 14 days for training remediation. This estimate is based on Army training doctrine and regulations (TRADOC Regulation 350-6) as well as clinical experience.(48)Complete calculations and assumptions can be found in **appendix F**.

Indirect costs (IDC) were calculated as the product of training costs per day and the sum of days lost because of disposition. Assumptions and calculations for this variable can be found in **appendix F** and **appendix G**.

Upon calculating both direct medical and indirect costs, both total cost (TC) and median cost (MC) were derived. Total cost included costs of medical resources to treat disease (clinic and hospital costs) and loss in productivity (sick in quarters or limited duty time). The MC was defined as the cost per patient treated. Assumptions and calculations for this variable can be found in **appendix G**.

Data analyses

All costs were compared with overall SSTI as well as *S.aureus* and MRSA SSTI specifically. For this analysis, both confirmed and probable cases were included in the *S.aureus* and MRSA SSTI estimates. A description of the methods used to generate these specific estimates was provided early (**Chapter 3, Part I**). Basic descriptive statistics (i.e. mean, median, and standard deviation) were computed for all cost variables included in the dataset. Sum of costs across predictor categories (age, sex, trainee status, etc.) were also calculated. Clinic, hospital, and lost-productivity costs estimates were calculated based on the previously described cost avoidance model (CAM) and guidance from the CDC's economic evaluations tutorials.(1; 33; 34; 115; 177) The cost calculations were modified to fit the scope of this COI analysis. Cost calculations are illustrated in **appendix G**.(1; 33; 34; 115; 177)

Univariate cost analyses were performed to assess the differences in total costs and median cost among baseline characteristics (demographics, infection type, disease management, and temporal variables). The statistical tests used included Mann-Whitney U or Kruskal-Wallace. The test used was dependent on the data variable type and the distribution of the cost.(54) All test for significance were two-tailed with $\alpha=0.05$. Analyses were performed using SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Multivariate cost analyses were used to determine potential predictors of costs as well as account for potential confounding variables (age, sex). A generalized linear model (GLM) using a gamma distribution with a log link function was used to perform this analysis.(199) The GLM was used because it offers a variety of distributions and link functions to choose from when the outcome variable has a non- normal distribution and the outcome is not linearly

related to the covariates.(23; 76) In this study, the outcome variable is continuous (total cost of illness) but has a non-normal distribution and the values are all positive. By meeting these two assumptions, the gamma distribution is an appropriate choice.(76) A log-link function was chosen because the covariates have a non-linear effect on the dependent variable. Furthermore, using this link function facilitates interpretation as opposed to log-transforming the dependent variable.(76) The model covariates act multiplicatively on the dependent variable.(23) Lastly, these methods have been used to perform analyses on similar data. (23) Model fit was determined by using goodness of fit measures (deviance ratio) as well as scatter plots of standardized deviance residual by predicted mean response(23; 83)

RESULTS

Baseline costs

Baseline, raw medical and pharmaceutical cost estimates for overall and MRSA-confirmed SSTI are shown in **table 17**. These costs do not incorporate all costs associated with the infection (i.e. inclusion of lost-time in training costs). On average, baseline medical costs per SSTI case were 251.83 ± 407.82 United States Dollars (USD). The sum of baseline medical costs for all SSTI cases was about 10.7 million USD. Pharmacy costs comprised about 7% of the baseline medical costs.

Direct medical care costs

Direct medical care costs (DMC) amounted to 9.98 Million (M) USD, almost one-quarter of the total costs related to overall SSTI (**table 18)**. These costs include costs related to clinical, hospital, and ER care. Median DMC for overall, *S.aureus*, and MRSA SSTI were 139.76 (IQR: 210.95), 153.00 (IQR: 260.17), and 159.32 (IQR: 302.50) USD. Total DMC (sum) increased steadily from 2006 through 2008 for overall SSTI with a 350,000 USD decline in 2009. Total DMC for *S.aureus* and MRSA SSTI peaked in 2008 with about a 500,000 and 240,000 USD decline in 2009 (**figure 27**). Median DMC for overall, *S.aureus* and MRSA followed similar trends with a peak in 2007 and a slight decline thereafter.

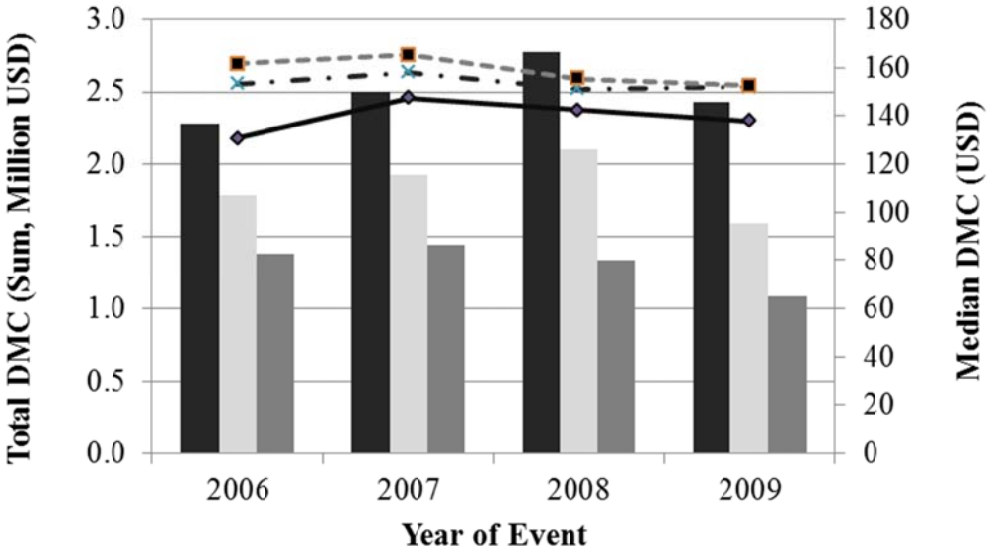


Figure 27 Annual total and median direct medical costs (DMC) of overall, S.aureus, and MRSA SSTI. Dark grey, light grey, and medium grey bars represent total DMC for overall, *S.aureus*, and MRSA SSTI, respectively. Light grey (square), medium grey (cross) and dark grey (Diamond) lines depict overall, SA, and MRSA SSTI, respectively. All costs are reported in United States Dollars (USD).

Total clinical care costs during the four-year period were estimated at 4.59 M USD- *S.aureus* and MRSA SSTI accounted for approximately 76% and 53% of these costs. The clinical care costs per infection for a *S.aureus* and MRSA SSTI were on average slightly higher than costs for overall SSTI (150 and 154 USD compared with 137USD, respectively) (**table 18**).

The sum of costs for hospital care during the four year period was 5.19 M USD; *S.aureus* and MRSA SSTI accounted for approximately 72% and 51% of these costs. For overall and *S.aureus* SSTI, the median costs per infection equated to 4867.57 (IQR: 5136.29). Average hospital care costs for MRSA SSTI was 4735.29 (IQR: 5300.35) (**table 18**).

Total clinical and hospital care costs for overall SSTI followed the same trends with costs peaking in 2008. For *S.aureus* and MRSA SSTI, total hospital costs peaked in 2008 and then declined by 36% and 23% in 2009, respectively. Median overall, *S.aureus* and MRSA SSTI hospital care costs were much higher than clinical care costs for the entire 4-year study period. MRSA SSTI had the highest median annual clinical and hospital care costs only in 2006 and 2007 (**figure 28**).

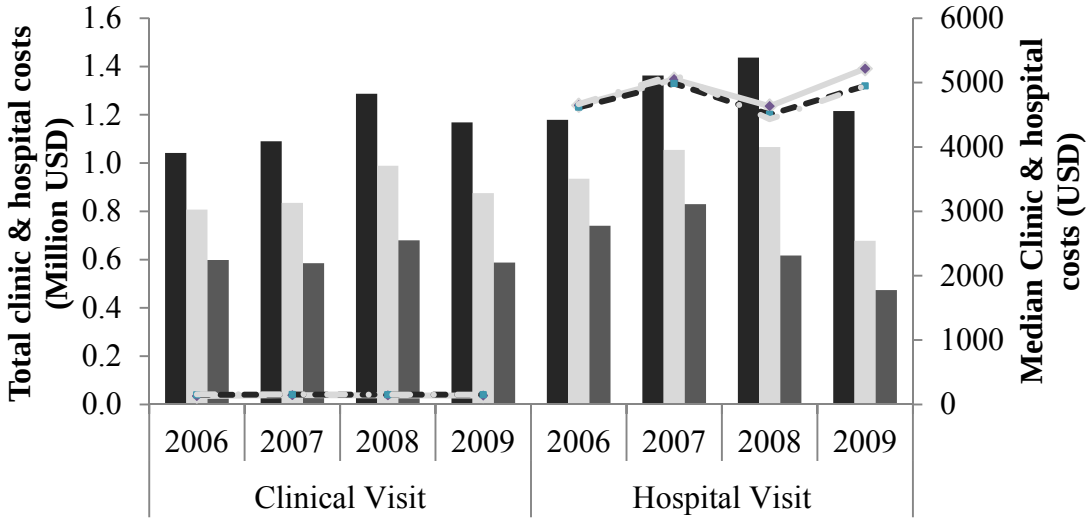


Figure 28 Annual total and median clinic and hospital costs of overall, S.aureus (SA), and MRSA SSTI. Dark grey, light grey, and medium grey bars represent total clinic and hospital costs for overall, *S.aureus*, and MRSA SSTI, respectively. Light grey, medium grey, and dark grey dashed lines depict *S.aureus* and MRSA SSTI as well as overall SSTI, respectively. All costs are reported in United States Dollars (USD).

Median DMC for *S.aureus* and MRSA SSTI among demographic categories such as sex, race, age, marital status, and education level were slightly higher than overall SSTI (**table 21a**). Additionally, the median DMC were evaluated among, installation, rank, and MOS (**table 21b**). These costs were found to be slightly higher among those assigned to Fort Knox or Fort Sill for training, lower rank (E01), those with "Armor" MOS, with a

Bachelor's degree and those experiencing an SSTI or MRSA SSTI in the first phase of training (**table 21a-21c**).

For overall, *S.aureus* and MRSA SSTI, analyses showed median DMC cost were found to be slightly higher among those diagnosed with a purulent SSTI compared to a non-purulent SSTI (**table 21c**). Additionally, having a MRSA culture contributed to over twice the direct medical care costs compared to those without any culture being obtained (347.03 and 125.80, respectively) (**table 21c**).

Last, *S.aureus* SSTI median DMC were slightly higher during phase 1 of training compared with phase 2. When evaluated by overall and MRSA SSTI, the opposite was observed (median DMC costs were slightly higher for those with an infection during the second phase of training). Seasonal trends were also evaluated. For all infection types, median DMC costs were not substantially different ranging between 134.13 (winter) and 161.32 (summer) per infection (**table 21c**).

Median DMC of overall, *S.aureus,* and MRSA SSTI were also analyzed by procedure and antibiotic coverage. Results showed that median DMC for an I&D were a lower when considering overall SSTI compared to *S.aureus* and MRSA-confirmed SSTI (378.88, 390.21, and 402.84 USD, respectively) ($p<0.001$). Furthermore, those with an I&D procedure had three times the median DMC cost compared to those without an I&D procedure, regardless of SSTI type ($p<0.001$). Additionally, median DMC were evaluated among those prescribed an antibiotic with and without MRSA coverage. Costs were about 35% higher with coverage as opposed to those without coverage (regardless of SSTI type). *S.aureus* and MRSA SSTI DMC costs were slightly more than the costs of overall SSTI alone among those with MRSA coverage (**table 21d**).

Indirect costs

Indirect costs (IDC) for the purposes of this study are those costs associated with time spent away from training. Two variables are necessary for the indirect cost calculation (a) time lost and (b) average trainee salary. Lost-time in training (LTT) encompasses several factors to include lost-time for clinical care, hospital care, "sick in quarters" disposition, and "limited duty" disposition as well as being recycled from training. Time was calculated earlier (Chapter 3, part I). Salary for a trainee consists of basic pay, recruiting costs, and training costs (**table 22**). Salary was computed as total costs per day of training. The trainee's salary is dependent on the trainee's rank during training; therefore, total costs per day of training ranged from 458.75 USD up to 561.5 USD. Overall the sum total cost of training during the study period was 162.6 M USD.

Overall, IDC amounted to 41.5 M USD (median=1123.01 (IQR: 1671.53)) over four years, contributing to 80% of the total costs. When evaluated by LTT categories, total IDC were highest among those with a work duty limitation (13.2 M USD), a clinical visit (10.2 M), and a recycle disposition (10.4 M). Median IDC were highest among those who were recycled (28,786.26 USD (IQR: 2726.70) (**tables 19-20, figure 29**). Recycled LTT costs comprised about one-quarter of the total IDC.

Sensitivity analyses were performed to evaluate the recycled population's effect on costs of being recycled and total IDC at 0, 14, and 21 days of remedial training (**tables 19-20**). Analyses showed recycled IDC ranged from a low of 7.62 M USD to a high of 11.9 M USD, making about a 20-25% contribution to the total lost time in training costs.

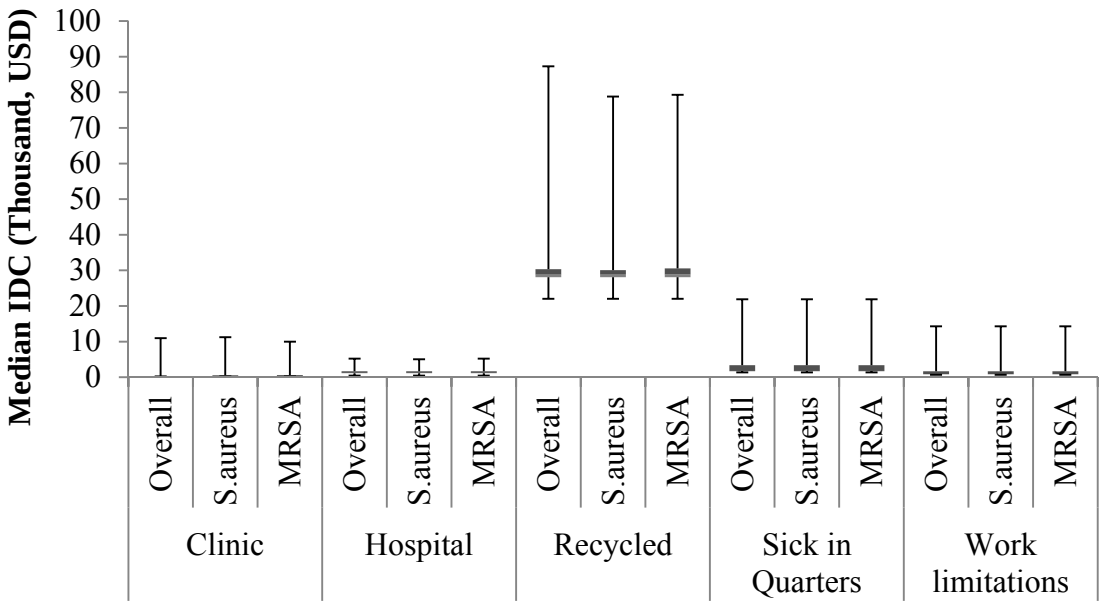


Figure 29 Overall, S.aureus and MRSA SSTI Indirect Costs (IDC) types. Median expressed by the grey bar. Error bars (capped lines) represent minimum and maximum values.

Median IDC varied with respect to demographic characteristics among those with overall, *S.aureus* and MRSA SSTI (**tables, 21a-21b**). For overall SSTI, median IDC do not seem to differ among sex, age, race, marital status or education level. Median IDC for *S.aureus* and MRSA SSTI appeared to be higher among females, "other" race group, married trainees, and those trainees with at least one semester of college. No median IDC differences were found among rank, location, and MOS variables for overall SSTI, which is opposite to what was observed for trainees with an *S.aureus* or MRSA- SSTI. Median IDC tended to be higher among trainees with a rank "E03", assigned to Fort Jackson, SC or Fort Sill, OK, and a "Armor" MOS.

Median IDC was also evaluated by temporal factors such as phase of training, season, and year of infection (**table 21c**). Results showed that median IDC, for overall SSTI, did not differ for any of these variables. In contrast, for both *S.aureus* and MRSA

SSTI, the cost varied among the respective categories. For instance, median IDC were higher among trainees experiencing either a *S.aureus* or MRSA SSTI during phase 1 of training as opposed to phase 2 (**figure 30**). Trainees with a MRSA-confirmed SSTI during phase 1 of training had the highest median IDC among all categories (p<0.001).

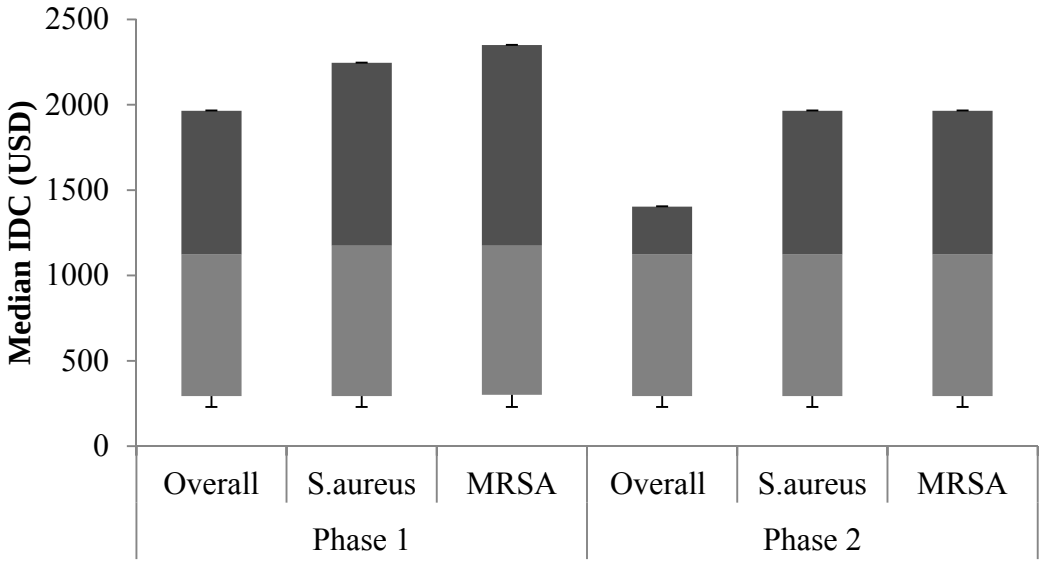


Figure 30 Median indirect costs (IDC) and phase of training. Error bars represent minimum values.

The median IDC were highest during the "summer" season and remained constant throughout the rest of the season categories for trainees with an *S.aureus* SSTI. The median IDC were the highest during both the "winter" and "summer" seasons for MRSA SSTI. The median IDC were also evaluated by with respect to the year the event occurred (**figure 31**). From 2006 through 2009, median LTT costs for *S.aureus* and MRSA SSTI ranged from about 1123 USD to 1174 USD, with peak costs being in 2007.

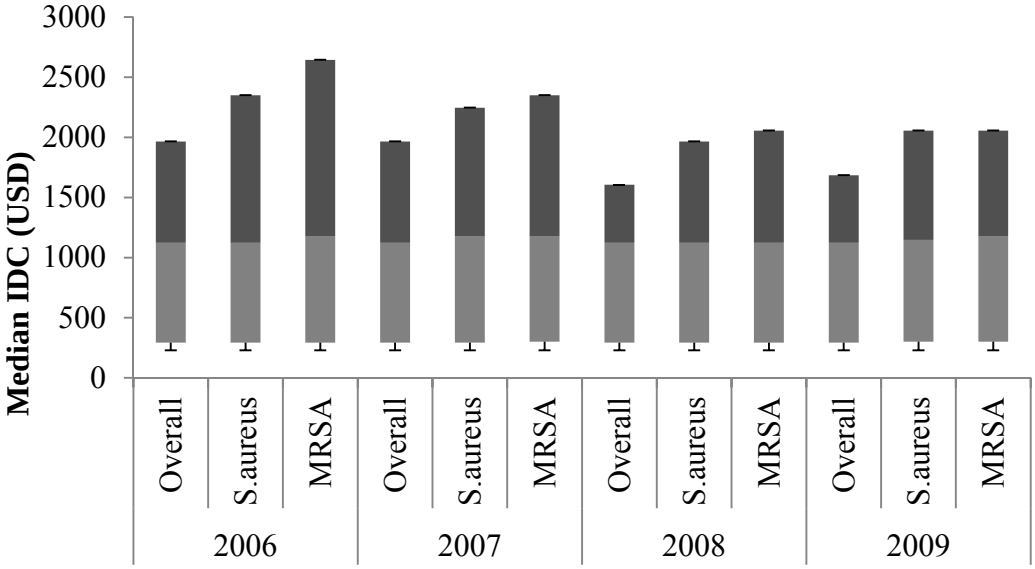


Figure 31 Annual median indirect costs (IDC) of overall, S.aureus and MRSA SSTI. Error bars represent minimum values.

Lastly, evaluations were performed to note any differences in median IDC and initial care received (microbiology, procedure, and antibiotic coverage) as well as clinical outcome (purulent and complicated SSTI) (**tables 21c and 21d**). Results showed that for overall, *S.aureus* and MRSA SSTI, median IDC were much higher for those with a complicated or purulent infection, clinically confirmed culture for MRSA, I&D procedure compared to those trainees without the procedure and slightly higher for those receiving an antibiotic with MRSA coverage as opposed to an antibiotic without MRSA coverage.

Total cost of illness (COI)

Total cost-of-illness (COI) is equivalent to the sum of direct medical care costs (clinical care, ER visit, and hospital care) and indirect costs (LTT costs). Overall total COI for overall, *S.aureus* and MRSA SSTI were 51.5 M, 39.7 M, and 27.7 M USD from 2006-2009, respectively. The median COI per overall, *S.aureus* and MRSA SSTI was

1231 (IQR: 1739), *S.aureus* 1265 (IQR: 1972) and MRSA SSTI was 2484.80 (IQR: 2088) USD, respectively.

Annually, from 2006 through 2008, total COI increased for trainees with overall and *S.aureus* SSTI, and then decreased in 2009. Median COI for these groups tended to stay relatively stable with costs between 1213.00 and 1239.00 USD. For the MRSA SSTI group, annual total COI decreased each year during the study period. MRSA SSTI experienced a steady decrease in median COI occurred from 2006 through 2009 as well (**figure 32**).

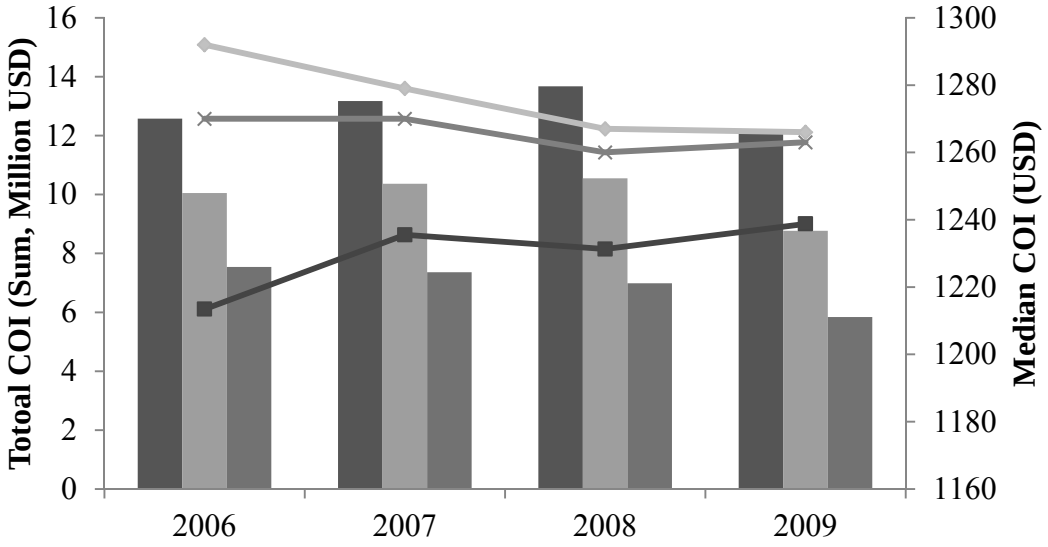


Figure 32 Annual cost-of-illnesses (COI) (sum and median) for overall, S.aureus and MRSA SSTI. Dark, light, and medium grey bars depict total COI for overall, *S.aureus* and MRSA SSTI, respectively. Light (diamond), medium (cross), and dark (square) grey lines represent MRSA and *S.aureus* SSTI in addition to overall SSTI, respectively.

Median COI for overall SSTI were significantly different among race ($p<0.001$), marital status ($p=0.001$), education level ($p<0.001$), rank ($p<0.001$), training ($p<0.001$), location ($p<0.001$), and MOS ($p<0.001$) categories. Upon further inspection, it appears that those in the 25-34 age category, “black” race, “Armor” MOS and assignment to

“Fort Sill” training installation had higher total COI per infection compared with other groups in these categories. Median COI seemed to be lower for those in the “black” race category.

Results showed that individuals with an SSTI overall who had experienced almost 2.5 the median COI compared with their counterparts (non-purulent SSTI) ($p<0.001$). Additionally, those same trainees with a complicated SSTI had 8 times the median COI compared to infections that resolved ($p<0.001$). A clinically confirmed culture for MRSA had about 2 times the median total COI per infection compared with no culture being obtained ($p<0.001$). Similar trends were observed among MRSA-confirmed SSTI patients ($p<0.001$).

Median COI was also evaluated by of the initial care received during a clinic visit. Trainees with overall, *S.aureus*, or MRSA SSTI who had an I&D procedure had twice the median COI compared with trainees who did not have such a procedure ($p<0.001$). Furthermore, this same group had slightly higher median COI if they received an antibiotic regimen with coverage for MRSA ($p<0.001$).

Univariate and multivariate analysis

Variables potentially associated with COI were explored through univariate analyses (UVA) using a generalized linear model with gamma distribution and a log-link function. Potential differences in the dependent variable (COI) among host-specific and temporal factors in additional to clinical outcomes and initial clinical care were evaluated for overall, *S.aureus* and MRSA SSTI. Initial analyses revealed demographic variables (sex, race, marital status, education, rank, training site, and MOS), temporal factors (phase of training and year of infection), clinical outcomes (purulent and complicated

SSTI and clinically confirmed MRSA culture), and initial care (I&D procedure and MRSA coverage) were associated COI ($p<0.001$). For SSTI overall, median COI was greater for females, trainees who are married, ranks of E2 or E3, and assigned to a training location other than Fort Benning. Additionally, those trainees with a clinical culture positive for MRSA, an incision and drainage (I&D) procedure, prescribed an antibiotic regimen suitable to treat MRSA, and a complicated SSTI, median COI was higher compared their counterparts. Lastly, African-American race, having an infection after 2006, and phase 2 of training were associated with lower COI compared to their referent values (**Tables 21a-21d**). To explore the direction of these associations, further multivariate analyses (MVA) were performed using the same methods as with the UVA.

Three models (overall, *S.aureus* and MRSA SSTI) were developed to evaluate the dependent COI variable's association with clinical outcomes (SSTI resolution and Microbiology), initial care (antibiotic regimen and procedure type), temporal factors (phase, season and year of event), and host-specific factors (training center, rank, sex, race, and age). Results showed an overall SSTI model that included the following potential predictors of a significant increase in COI ($p<0.001$): complicated SSTI, clinically confirmed MRSA culture, MRSA coverage, I&D, training site (Ft Jackson, SC; Ft Knox, KY, and Ft Sill, OK), and age (25-34). Betas showed two times an increase in COI for a complicated SSTI compared with an SSTI that resolved (table 3.5) (B=2.35; 95%CI (2.29, 2.41, $p<0.001$). COI increased by 44% if an infection was associated with a clinically confirmed MRSA culture. Additionally, having an incision and drainage procedure increased cost by 58% compared to not having such a procedure. In the same model, potential predictors associated with a decrease in total COI of SSTI overall were

phase of training (two), year of infection (2008), rank (E04), and race (African American). Compared to phase one in training, the COI for phase two was reduced by 26% [B=-0.26, 95%CI (-0.29,-0.24)]. Individuals with a rank of E04 experienced significantly less costs compared to those trainees with a rank of E01 (the lowest rank for a trainee). When evaluating year of event, trainees with an SSTI overall in 2008 experienced less cost than those with an infection in 2006. Lastly, COI decreased by 20% for African American trainees compared to Caucasian trainees (**table 23**).

MVA using the same techniques to derive the overall SSTI model were also performed to evaluate the effects of variables on total COI related to *S.aureus* and MRSA SSTI specifically. Such analyses were done to determine if there was a difference in the predictors associated with overall SSTI COI and those costs associated with *S.aureus* and MRSA SSTI. The dependent variable (COI) and covariates used to develop the *S.aureus* and MRSA SSTI COI models were similar to the overall SSTI COI model, except microbiology, antibiotic regimen, and procedure type were not included in the model. (**Table 23**). The final *S.aureus* SSTI model showed increased Betas for complicated SSTI, training location (Ft Jackson, Ft Knox, Ft, Leonard Wood, and Ft Sill), rank (E02), sex (female), and age (25-34). Decreased betas were observed for training phase (two), season (fall/winter), rank (E04), and race (African American). (**Table 23**) Compared to the overall SSTI model, the *S.aureus* model was only slightly improved. The deviance ratio moved slightly closer to 1, but scatter plots only varied slightly. Additionally, betas were relatively the same in both of the models as well as 95%CI and p-values. Slight differences were observed with respect to the year of event and training center. (**Table 23**) Additionally, betas were much lower in the 'African American' race group in the

S.aureus model compared to the SSTI overall model. Lastly, Sex was the only factor dropped from the Overall SSTI model that remained in the *S.aureus* model.

The MRSA SSTI model resembled the *S.aureus* model. Results showed similar results with respect to the betas among the covariates and their 95% confidence intervals. The model showed increased COI for those trainees with a complicated infection. Additionally, COI was higher at Ft Jackson, Ft Knox, Ft Leonard Wood, and Ft Sill compared to Ft Benning. "Female" sex and older age were also associated with increased COI. Training phase 2, 'fall/winter' season, event year beyond 2006, rank (E04), and race (African American) were all associated with reduced COI. (**Table 23**)

Table 17 Overall SSTI baseline cost[1] estimates

	n[2]	**Mean (Min, Max) ± SD (USD)**	**Median (USD), IQR**	**Sum (USD)**
Baseline medical cost estimates	20,616	520.43 (1.25,188936.84) ±2381.11	147.16 (231.56	10,729,244.33
Baseline pharmacy cost estimates	20,314	39.70 (0.01,1023.18) ±58.81	21.49, 40.06	806,549.26

[1]Cost estimates are only summarized raw estimates and do not include factors associated with the main burden categories (direct and indirect medical costs). [2]Records without cost information were coded as missing instead of 0 to avoid underestimation of costs.

Table 18 Total direct medical and indirect costs estimates of overall SSTI

	Cost of Illness (USD) (direct medical + indirect costs)				
	Total Costs	**Direct medical costs**			**Indirect costs**
		Clinic	Hospital	ER	LTT
n	20,884	20,507	722	582	20,884
Mean	2467.52	223.74	7194.50	333.13	1989.79
SD	6288.12	252.32	9765.83	251.45	4556.89
Median	1230.51	136.53	4867.57	261.29	1123.01
IQR	1739.39	191.68	5136.29	288.76	1671.53
Sum	**51,529,131.46**	**4,588,179.62**	**5,194,427.56**	**193,880.81**	**41,552,796.46**

[1]All costs are reported as U.S. dollars; all measures reported (mean and median) are unadjusted; Standard deviation (SD); Interquartile range (IQR)

Table 19 Total indirect costs (lost-time in training) of overall SSTI

	Total lost time in training costs (USD)						
	Total Costs	**Clinic**	**Hospital**	**ER**	**SIQ**	**WDL**	**Recycle**
n	**20,883**	20,801	381	588	2,644	10,518	354
Mean	**1989.79**	495.07	1308.63	533.90	2534.34	1262.43	29557.20
SD	**4556.89**	567.43	495.03	944.19	1654.81	852.37	3762.28
Median	**1123.01**	293.73	1202.41	293.74	1762.4	881.21	28786.26
IQR	**1110.0**	280.75	2322.4	39.7	1684.5	421.13	2726.7
Sum	**41,552,796**	10,298,014	498,586	313,934	6,700,783	13,278,228.59	10,463,250

[1]All costs are reported as U.S. dollars; all measures reported (mean and median) are unadjusted; Standard deviation (SD); Interquartile range (IQR)

Table 20 Sensitivity analysis of costs when recycled at 0,14, and 21 days remedial training

	Cost of recycle from training			Cost of Lost time in training		
	0	**14**	**21**	**0**	**14**	**21**
n		354			354	
Mean	21,539	29,557.20	33,566.25	1853.87	1989.79	2057.75
SD±	3615.29	3762.28	3849.40	3637.64	4556.89	5033.60
Median	20,561.62	28,786.26	32,898.59	1123.01	1123.01	1123.01
IQR	2270.37	2262.73	2262.73	1671.53	1671.53	1671.53
Sum	**7,620,264**	**10,463,250.16**	**11,882,453.80**	**38,714,389**	**41,552,796**	**42,972,000**

[1]All costs are reported as U.S. dollars; all measures reported (mean and median) are unadjusted; Standard deviation (SD); Interquartile range (IQR)

Table 21a Median direct and indirect costs[1] of overall, *S.aureus* and MRSA SSTI among demographic factors

Factor[3]	Overall SSTI Median (IQR) Costs (USD) N=20,884			*S.aureus* SSTI Median (IQR) Costs (USD) N=14,243			MRSA SSTI Median (IQR) Costs (USD) N=9,522		
	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]
Sex									
Male	136.53 (210)	1123.01 (1672)	1235 (1732)	151.34 (256)	1123.01 (1762)	1264 (1927)[5]	153.01 (274)	1146.84 (1810)	1270 (2029)[5]
Female	149.57 (211)	1123.01 (1672)	1207 (1792)	171.86 (291)	1174.95 (2111)	1282 (2443)	182.62 (361)	1174.95 (2712)	1323 (3126)
Age									
17-24	136.55 (207)	1123.01 (1672)	1230 (1232)	152.67 (257)	1123.01 (1762)	1264 (1947)	158.27 (277)	1174.95 (1810)	1271 (2062)
25-34	138.82 (218)	1123.01 (1672)	1232 (1750)	151.69 (273)	1123.01 (1804)	1261 (2036)	156.72 (314)	1174.95 (1945)	1279 (2177)
Race									
White	153.00 (249)	1123.01 (1672)	1250 (1919)[5]	177.97 (313)	1174.95 (2056)	1305.74 (2337)[5]	196.15 (336)	1174.95 (2233)	1341 (2634)[5]
Black	251.18 (110)	1123.01 (909)	1194 (964)	112.82 (128)	1123.01 (909)	1218.30 (1093)	111.78 (129)	1123.01 (909)	1219 (1072)
Other	1656 (276)	1123.01 (1762)	1263 2040	193.77 (364)	1174.95 (2507)	1327 (2748)	229.60 (492)	1174.95 (2855)	1373 (3270)
Marital Status									
Single	136.43 (204)	1123.01 (1671)	1226 (1721)[5]	151.84 (250)[5]	1123.01 (1762)	1261 (1921)[5]	155.45 (270)	1123.01 (1810)	1267 (2032)[5]
Married	144.18 (232)	1123.01 (1762)	1247 (1817)	166.73 (298)	1175 (1945)	1290 (2146)	174.35 (338)	1174.95 (2226)	1319 (2533)
Education									
HS Diploma	135.40 (203)	1123.01 (1672)	1238 (1741)[5]	151.34 (252)	1174.95 (1762)	1268 (1972)[5]	151.34 (252)	1174.95 (1762)	1271 (2060)[5]

Factor [3]	Overall SSTI Median (IQR) Costs (USD) **N=20,884**			*S.aureus* SSTI Median (IQR) Costs (USD) **N=14,243**			MRSA SSTI Median (IQR) Costs (USD) **N=9,522**		
	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]
Equivalency Test	144.76 (223)	1123.01 (1672)	1584 (1774)	160.96 (285)	1123.01 (1810)	1265 (2064)	160.96 (285)	1123.01 (1810)	1287 (2280)
Bachelor's degree	137.86 (214)	917.47 (1376)	985 (1390)	158.21 (243)	917.47 (1376)	1012 (1502)	158.21 (243)	917.47 (1376)	1049 (1560)
One semester of College	136.16 (194)	1174.95 (1665)	1261 (1750)	160.51 (252)	1174.95 (1804)	1293 (1999)	160.51 (252)	1174.95 (1804)	1305 (2253)

[1]All costs are reported as U.S. dollars; all measures reported (median) are unadjusted; Standard deviation (SD); Interquartile range (IQR) [2] Univariate analyses were performed using non-parametric methods (Mann-Whitney U or Kruskal Wallace depending on the independent categorical variable). [3]Factors were evaluated for significance, those factors with p-values <0.05 were included in subsequent multivariate analyses. [4]Median (Interquartile range) Direct medical costs (DMC), Indirect medical costs (IDC), and Cost of Illness (COI) [5] Dependent variable is Total Costs (DMC+IDC); considered significantly different at $\alpha<0.05$; $p<0.05$

Table 21b Median direct and indirect costs[1] of overall, *S.aureus* and MRSA SSTI by demographic factors[2]

Factor [3]	Overall SSTI Median (IQR) Costs (USD) **N=20,884**			*S.aureus* Median (IQR) Costs (USD) **N=14,243**			MRSA Median (IQR) Costs (USD) **N=9,522**		
	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]
Rank									
E01	139.56	1123.01	1204	155.50	1123.01	1240	160.71	1123.01	1247
	(213)	(1685)	(1713)[5]	(219)	(1685)	(1994)[5]	(288)	(1965)	(2089)[5]
E02	139.63	1174.95	1257	156.65	1174.95	1294	160.71	1174.95	1299
	(210)	(1762)	(1794)	(264)	(1762)	(2038)	(275)	(2056)	(2141)
E03	132.58	1202.41	1269	145.78	1202.41	1298	152.58	1202.41	1313
	(203)	(1804)	(1775)	(243)	(1804)	(1925)	(276)	(1804)	(2094)
E04	136.70	917.47	984	153.80	917.45	1010	172.46	917	1020
	(215)	(1376)	(1360)	(242)	(1376)	(1525)	(308)	(1376)	(1606)
Location									
Fort Benning	122.58	1123.01	1216	141.45	1123.01	1246	142.49	1123.01	1251
	(188)	(1209)	(1563)[5]	(223)	(1672)	(1784)[5]	(237)	(1762)	(1895)[5]
Fort Jackson	143.74	1123.01	1241	165.02	1174.95	1276	167.86	1174.95	1289
	(205)	(1762)	(1827)	(261)	(2000)	(2230)	(283)	(2233)	(2565)
Fort Knox	162.57	1123.01	1261	210.18	1123.01	1290	221.88	1123.01	1304
	(252)	(1672)	(1797)	(310)	(1762)	(1952)	(322.14)	(1810)	(2101)
Fort Leonard Wood	103.09	1123.01	1190	129.50	1123.01	1234	133.02	1123.01	1250
	(203)	(1209)	(1611)	(286)	(1762)	(1998)	(321)	(1769)	(2050)
Fort Sill	160.57	1123.01	1277	186.82	1174.95	1235	203.10	1174.95	1326
	(204)	(1672)	(1786)	(284)	(1756)	(1913)	(298)	(1804)	(1986)
MOS									
Infantry	133.61	1123.01	1233	143.74	1123.01	1265	145.03	1174.95	1270
	(201)	(1469)	(1691)[5]	(234)	(1762)	(1861)[5]	(247)	(1810)	(1988)[5]
Logistics	132.58	1123.01	1247	135.59	1174.95	1271	138.18	1174.95	1271
	(168)	(1672)	(1754)	(214)	(1804)	(1986)	(219)	(1945)	(2076)

Factor [3]	Overall SSTI Median (IQR) Costs (USD) **N=20,884**			*S.aureus* Median (IQR) Costs (USD) **N=14,243**			MRSA Median (IQR) Costs (USD) **N=9,522**		
	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]
Medical	134.48 (203)	1123.01 (1110)	1196 (1439)	154.46 (280)	1123.01 (1672)	1235 (1830)	164.89 (309)	1123.01 (1672)	1242 (1841)
Communications	118.79 (197.85)	1123.01 (1175)	1199 (1395)	137.34 (265)	1123.01 (1672)	1225 (1748)	136.88 (276)	1123.01 (1672)	1231 (1909)
Artillery	162.48 (212.21)	1123.01 (1672)	1260 (1832)	196.72 (286)	1174.95 (1762)	1326 (2017)	203.10 (312)	1174.95 (1952)	1326 (2094)
Armor	229.69 (303.80)	1123.01 (1762)	1303 (2073)	274.82 (406)	1174.95 (2056)	1363 (2349)	268.60 (487)	1174.95 (2141)	1397 (2912)

[1]All costs are reported as U.S. dollars; all measures reported (median) are unadjusted; Standard deviation (SD); Interquartile range (IQR) [2] Univariate analyses were performed using non-parametric methods (Mann-Whitney U or Kruskal Wallace depending on the independent categorical variable). [3]Factors were evaluated for significance, those factors with p-values <0.05 were included in subsequent multivariate analyses. [4]Median (Interquartile range) Direct medical costs (DMC) and Indirect medical costs (IDC) [5] Dependent variable is Total Costs (DMC+IDC); considered significantly different at $\alpha<0.05$; $p<0.001$

Table 21c Median direct and indirect costs[1] of overall, *S.aureus* and MRSA-confirmed SSTI among temporal and clinical outcomes[2]

Factor [3]	Overall SSTI Median (IQR) Costs (USD) **N=20,884**			*S.aureus* Median (IQR) Costs (USD) **N=14,243**			MRSA Median (IQR) Costs (USD) **N=9,522**		
	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]
Training Phase									
Phase 1 (BCT)	133.65	1123.01	1241	153.28	1174.95	1274	158.15	1174.95	1286
	(218)	(1672)	(1806)[5]	(278)	(1952)	(2131)[5]	(300)	(2049)	(2237)[5]
Phase 2 (AIT)	143.74	1123.01	1191	152.36	1123.01	1244	161.37	1123.01	1256
	(190)	(1110)	(1397)	(227)	(1672)	(1739)	(257)	(1672)	(1830)
Season									
Winter	134.13	1123.01	1230	150.40	1123.01	1265	148.50	1174.95	1282
	(207)	(1672)	(1698)	(265)	(1762)	(1911)	(292)	(1756)	(2003)
Spring	137.76	1123.01	1223	153.00	1123.01	1259	161.03	1123.01	1268
	(215)	(1672)	(1750)	(260)	(1762)	(2007)	(291)	(1952)	(2173)
Summer	139.70	1123.01	1236	156.81	1174.95	1272	161.32	1174.95	1284
	(224)	(1672)	(1805)	(277)	(1952)	(2134)	(295)	(2056)	(2264)
Fall	136.43	1123.01	1229	151.20	1123.01	1259	158.14	1123.01	1267
	(191)	(1391)	(1636)	(231)	(1672)	(1775)	(253)	(1762)	(1851)
Year of infection									
2006	130.78	1123.01	1213	153.34	1123.01	1270	161.50	1174.95	1292
	(224)	(1672)[5]	(1838)	(292)	(2056)	(2438)[5]	(317)	(2350)	(2733) [5]
2007	147.12	1123.01	1236	158.01	1174.95	1270	165.17	1174.95	1279
	(225)	(1672)	(1793)	(255)	(1952)	(2065)	(268)	(2049)	(2198)
2008	139.54	1123.01	1231	151.27	1123.01	1260	155.61	1123.01	1267
	(206)	(1312)	(1694)	(266)	(1672)	(1816)	(295)	(1762)	(1901)
2009	134.55	1123.01	1239	151.98	1146.84	1263	152.67	1174.95	1266
	(196)	(1391)	(1669)	(234)	(1756)	(1804)	(252)	(1756)	(1821)
SSTI type									
Purulent	147.75	1123.01	1251	159.32	1174.95	1273	161.05	1174.95	1278

	(236)	(1762)	(1845)[5]	(280)	(1810)	(2061)[5]	(290)	(1952)	(2123)[5]
Non-purulent	122.65	300.60	522	125.66	300.60	682	122.54	300.60	492
	(112)	(894)	(931)	(119)	(894.2)	(970)	(125)	(894)	(966)
Status									
Resolved	135 .05	1123.01	1216	148.07	1123.01	1251	150.85	1123.01	1258
	(187)	(1209)	(1561)[5]	(223)	(1672)	(1788)[5]	(240)	(1762)	(1843)[5]
Complicated	4642.05	6176.57	10,834	4513.00	6613.23	11,105	4642	6457.32	11,104
	(5186)	(29,080)	(33,520)	(4722)	(28962)	(33,309)	(5138)	(29,074)	(33,551)

[1]All costs are reported as U.S. dollars; all measures reported (median) are unadjusted; Standard deviation (SD); Interquartile range (IQR) [2] Univariate analyses were performed using non-parametric methods (Mann-Whitney U or Kruskal Wallace depending on the independent categorical variable). [3]Factors were evaluated for significance, those factors with p-values <0.05 were included in subsequent multivariate analyses. [4]Median (Interquartile range) Direct medical costs (DMC) and Indirect medical costs (IDC) [5] Dependent variable is Total Costs (DMC+IDC); considered significantly different at $\alpha<0.05$.

Table 21d Median direct and indirect costs1 of overall, S.aureus and MRSA SSTI and initial clinical care2

	Overall SSTI Median (IQR) Costs (USD)			*S.aureus* Median (IQR) Costs (USD)			MRSA Median (IQR) Costs (USD)		
Factor [3]	**N=20,884**			**N=14,243**			**N=9,522**		
	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]	DMC[4]	IDC[4]	COI[5]
Microbiology									
No culture	125.80 (152)	1123.01 (909)	1183 (1140)[5]	129.60 (181)	1123.01 (1175)	1213 (1392)[5]	128.90 (187)	1123.01 (1175)	1216 (1422)[5]
Culture other	150.85 (234)	1123.01 (1672)	1215 (1771)	-	-	-	-	-	-
Culture MSSA	270.39 (392)	1468.69 (2374)	1951 (2574)	270.39 (392)	1468.69 (2330)	1951 (2574)	-	-	-
Culture MRSA	348 (501)	2056.16 (3283)	2481 (3999)	348.08 (501)	2056.16 (3283)	2481 (3999)	348.08 (501)	2056.16 (3283)	2481 (3999)
Procedure									
Incision & drainage	378.88 (472)	1965.27 (2776)	2367 (3281)[5]	390.21 (481)	2056.16 (2808)	2434 (3370)[5]	402.84 (498)	2056.16 (3085)	2500 (3597)[1]
Other procedure	120.20 (127)	1123.01 (909)	1177 (1045)	124.81 (144)	1123.01 (1110)	1200 (1233)	123.78 (146)	1123.01 (1110)	1202 (1217)
Antibiotic Regimen[6]									
MRSA Coverage	168.37 (278)	1174.95 (1952)	1291 (2153)	188.02 (318)	1174.95 (2226)	1345 (2451)[5]	200.25 (339)	1174.95 (2405)	1378 (2622)
No MRSA Coverage	122.53 (135)	917.47 (909)	1151 (1143)	127.56 (148)	1123.01 (1110)	1203 (1301)	121.01 (158)	1123.01 (1110)	1175 (1214)

[1]All costs are reported as U.S. dollars; all measures reported (median) are unadjusted; Standard deviation (SD); Interquartile range (IQR)
[2] Univariate analyses were performed using non-parametric methods (Mann-Whitney U or Kruskal Wallace depending on the independent categorical variable).
[3]Factors were evaluated for significance, those factors with p-values <0.05 were included in subsequent multivariate analyses.
[4]Median (Interquartile range) Direct medical costs (DMC) and Indirect medical costs (IDC)
[5] Dependent variable is Total Costs (DMC+IDC); considered significantly different at $\alpha<0.05$.
[6]MRSA coverage includes TMP-SMX, Doxycycline, tetracycline, minocycline, and clindamycin antibiotic type prescriptions. Non-MRSA coverage includes cephalosporin, amoxicillin, and quinolone antibiotic type prescriptions.

Table 22 Overall recruit salary and training costs by rank (Trainee first incident case only)

	N 20,844	**E1 (n=9446)** Cost (USD)	**E2 (n=6282)** Cost (USD)	**E3 (n=4045)** Cost (USD)	**E4 (n=1110)** Cost (USD)
Basic pay (a)		$17,891.31	$20,055.60	$21,349.53	$25,803.45
Recruiting costs (b)		$23,327.73	$23,399.12	$23,352.53	$3549.55
Training costs (c)		$17,739.08	$18,230.13	$18,424.25	$18,814.43
Overall costs for trainee (a+b+c)		**$58,958.12**	**$61,684.5**	**$63,126.31**	**$48,167.43**
Salary per day(d) of training		$170.39	$191.01	$203.33	$245.75
Training cost per day (e) of training		$168.94	$173.62	$175.47	$179.19
Recruiting costs per day (f) of training		$222.17	$222.85	$222.41	$33.81
Total costs per day of training (d+e+f)		**$561.5**	**$587.48**	**$601.21**	**$458.75**
Overall costs by rank per day of training (n)* (d+e+f)*105		**$556,912,545.00**	**$387,507,682.80**	**$255,348,917.25**	**$53,467,312.50**

Table 23 Factors associated with total costs of illness for SSTI overall, final multivariate model[1,2]

		Overall SSTI Model					*S.aureus* SSTI Model					MRSA SSTI Model				
Factor		n	Mean	B	95% CI	p-value	n	Mean	B	95% CI	p-value	n	Mean	B	95% CI	p-value
Clinical Outcomes																
Resolution	Resolve	14436	1849	**Ref**			13333	2051	**Ref**			8907	1821	**Ref**		
	Complicate	742	19386	2.35	2.29,2.41	0.000	645	19057	2.43	2.36,2.50	0.00	448	19847	2.39	2.31,2.47	0.00
Microbiology	No culture	11325	4795	Ref												
	Other organism	521	5429	0.12	0.05,0.20	0.001										
	MSSA	1006	6625	0.32	0.27,0.38	0.000										
	MRSA	2326	7451	0.44	0.40,0.48	0.001										
Initial care																
Antibiotic	No coverage	2318	5374	-0.22	-0.25,-0.18	0.000										
	MRSA Coverage	12860	6671	**Ref**												
Procedure type	I&D	3750	7995	0.58	0.55,0.61	0.000										
	Other procedure	11428	4484	**Ref**												
Temporal factors																
Training phase	Phase 1	9901	6831	**Ref**			9331	7185	**Ref**			6242	6749	**Ref**		
	Phase 2	5277	5248	-0.26	-0.29,-0.24	0.000	4647	5440	-0.25	-0.28,-0.22	0.000	3113	5356	-0.23	-0.27,-0.19	0.000
Season	Fall/winter	5763	5866	-0.04	-0.07,-0.014	0.003	5347	6252	-0.05	-0.08,-0.02	0.003	3607	5869	-0.05	-0.09,-0.011	0.011
	Spring/summer	9415	6111	**Ref**			8631	6252	**Ref**			5748	6160	**Ref**		
Year	2006	3679	6178	**Ref**			3219	6588	**Ref**			2246	6626	**Ref**		
	2007	3819	6102	-0.012	-0.05,0.03	0.509	3380	6288	-0.07	-0.11,-0.03	0.002	2261	6175	-0.07	-0.12,-0.02	0.007
	2008	4111	5597	-0.099	-0.14,-0.06	0.000	3872	5780	-0.16	-0.20,-0.12	0.000	2545	5524	-0.18	-0.23,-0.13	0.000
	2009	3569	6090	-0.014	-0.05,0.02	0.463	3507	6380	-0.11	-0.15,-0.06	0.000	2303	5781	-0.14	-0.19,-0.08	0.000
Host-specific factors																
Training center	Fort Benning	4399	5388	**Ref**			4203	5557	**Ref**			2846	5274	**Ref**		
	Fort Jackson	4771	7240	0.30	0.26,0.33	0.000	4383	7515	0.31	0.27,0.35	0.000	2910	7062	0.29	0.24,0.34	0.000
	Fort Knox	1586	6355	0.17	0.12,0.21	0.000	1340	6587	0.13	0.07,0.18	0.000	866	6112	0.15	0.08,0.22	0.000
	Fort Leonard	2665	5398	0.00	-0.04,0.04	0.925	2409	5803	0.12	0.07,0.17	0.000	1626	5847	0.10	0.05,0.16	0.000
	Fort Sill	1757	5749	0.07	0.02,0.11	0.005	1643	5984	0.13	0.08,0.18	0.000	1107	5903	0.11	0.05,0.17	0.000
Rank	E01	7029	6226	**Ref**			6358	6518	**Ref**			4242	6187	**Ref**		
	E02	4557	6425	0.03	0.001,0.06	0.042	4247	6742	0.04	0.01,0.08	0.020	2831	6366	0.03	-0.01,0.07	0.182
	E03	5875	6440	0.03	-0.002,0.07	0.063	2719	6797	0.02	-0.02,0.06	0.380	1801	6427	0.04	-0.01,0.09	0.127
	E04	717	4988	-0.22	-0.29,-0.16	0.000	654	5115	-0.22	-0.30,-0.15	0.000	481	5162	-0.18	-0.27,-0.10	0.000
Sex	Male	13202	6007				12296		Ref			8226	2834	**Ref**		
	Female	1978	5820				1682		0.09	0.04,0.13	0.000	1129	3473	0.14	0.08,0.20	0.000
Race	White	11298	6436	**Ref**			9601	6470	**Ref**			6337	6961	**Ref**		
	Black	3291	5289	-0.20	-0.23,-0.16	0.000	3870	5946	-0.41	-0.45,-0.38	0.000	2702	4484	-0.44	-0.48,-0.40	0.000
	Other	589	6305	-0.02	-0.09,0.05	0.551	507	6352	0.01	-0.07,0.09	0.864	316	6963	0.00	-0.10,0.10	0.995
Age	17-24	13039	5651	**Ref**			11944	5980	**Ref**			7975	5680	**Ref**		
	25-34	2139	6344	0.12	0.08,0.15	0.000	2034	6536	0.10	0.06,0.14	0.000	1380	6364	0.11	0.06,0.17	0.000

[1]A generalized linear model with negative binomial distribution was used to evaluate a parameter's effect on the lost time in training burden estimate. Dependent Variable: Lost time in training. Gray areas indicate variables that were not included in the final model.

DISCUSSION AND CONCLUSION (CHAPTER 3 PART I AND II)

This comprehensive, 4-year evaluation across all Army recruit training sites revealed high burden in terms of rates of infection, days lost in training and costs associated with care as well as time spent away from training for overall, *S.aureus* and MRSA SSTI. Three major findings resulted from this analysis. First, the proportion of SSTI cultured was so low that rates for culture-confirmed *S.aureus* and MRSA SSTI were extremely underestimated. Evidence-based methodology was incorporated into the study to derive probable *S.aureus* and MRSA SSTI estimates that accurately reflected the actual disease burden within the recruit training population. Second, training remediation (also known as being recycled) because of infection significantly contributed to lost-time in training as well as days lost from work limitations. Furthermore, indirect costs comprised 80% of the total COI, which showed the importance of this estimate in cost calculations. All of these findings are relevant for both clinical and operational environments and strengthen the case for primary prevention of these infections. The burden associated with lost time in training and indirect costs combined, adds to the evidence that primary prevention of these infections is necessary. Results from this study revealed that most resources are being consumed through hospitalization, convalescence, and training remediation. By keeping a healthy person disease free, such measures can be avoided.

Rates of *S.aureus* and MRSA-confirmed SSTI were underestimated. One notable contributor to this underestimation was the SSTI culture rate. Rates ranged from 21% for purulent SSTI and 19% for non-purulent SSTI. These rates are below the national average (47-73%) (137; 207) and military average (30-54%) (65; 203) for purulent SSTI.

On average, the proportion of non-purulent SSTI cultured nationally ranges from 15-16% (44). Additionally, SSTI cases were identified based on ICD-9-CM codes as opposed to clinical diagnosis. A disconnect could have occurred between the link of the clinical culture and ICD-9-CM code. This result could mean that many *S.aureus* and MRSA SSTI cases could have been missed. Considering the number of *S.aureus* and MRSA SSTI cases that were potentially underestimated, lower infection rates (compared with the literature) were obtained with respect to the military population. Using evidence from multiple resources (13; 44; 61; 65; 86; 87; 114; 118; 137; 146; 203; 207), sensitivity analyses were performed to conservatively estimate the number of "probable" *S.aureus* and MRSA SSTI cases that could be missed because of lack of culture. Analyses revealed that rates for *S.aureus* and MRSA- confirmed SSTI were two to three times as low as their probable counterparts. Total confirmed cases for *S.aureus* and MRSA SSTI were 4,154 and 2,819, respectively; an additional 10,000 *S.aureus* and 6,700 MRSA-probable SSTI cases were found after assumptions were applied to calculate probable cases.

Since using the lost time in training metric is a novel approach to estimating the overall, *S.aureus* and MRSA SSTI burden in the recruit training population, little literature is available to compare results. The most recent military surveillance reports from 2012 and 2013 have shown lost work time estimates for the recruit training populations among all service-specific training sites combined.(14; 16) Between 4,500 and 6,000 days of work were lost (per year) between 2011 and 2013 in this population. Lost-work time accounted for 6.3% of the total lost work time among recruit trainees in 2013 compared with 3.0% of total lost work time among the entire active duty population.(16) These figures do not account for time lost because of being "recycled";

therefore, the estimates from the literature are lower than what was found in this current study (1; 21; 33; 48). The methods by which they calculated lost work time were also different as they only accounted for lost ambulatory care time if the medical encounter included a limited-duty disposition. Regardless, among trainees, skin diseases ranks fourth with respect to illness burden (medical encounters and individuals affected) within this population and fifth in terms of lost-work time. (14; 18)

This study used a cost of illness framework to estimate the economic burden of overall and MRSA SSTI specifically within the Army active duty recruit training population. Only one recent study by Lee et al. (2013) used cost of illness methodology to evaluate the economic burden of community-acquired MRSA (CA-MRSA) in the military overall (no known studies evaluated only overall SSTI).(120) They evaluated the literature and obtained rate estimates within the military population to calculate costs from the third-party payer and societal perspectives. They performed a sensitivity analysis in which the rates range from a low of 15 per 1000 to a high of 35 per 100 cases of CA-MRSA. They found costs from the third-party and societal perspectives ranged from 14-32 and 16-36 million US dollars (USD) per year for the entire military population. Our study showed with a MRSA SSTI incidence rate of 98.0 per 100 training-cycles among recruit trainees, total costs were approximately 19.3 million USD over the four-year study period. Using the results from Lee, we can expect that from a third-party payer perspective, MRSA SSTI among recruits contributes from 15-34% of the costs and 13-30% of the costs from a societal perspective. Indirect costs comprised the majority of the total cost of illness in our study. In the Lee study, it is difficult to discern the direct and indirect costs specifically. This current study used sensitivity

analysis to evaluate the effect of being “recycled” from 0-21days remedial training on total costs. Results showed costs ranged from 13-18 million USD for MRSA SSTI. If indirect costs were actually included within the Lee study, total cost of illness should have been higher.

The recycled population, although small, contributes substantially to lost time in training and the cost of illness. Significant differences in both lost time in training and the cost of illness for of overall, *S.aureus* and MRSA SSTI were found among those who were “recycled” compared with those who were not “recycled”. This is an important finding in that the literature tends to focus on direct medical costs, but the economic burden lies in the indirect, lost productivity costs. Lost time for remediation considered the length of stay in the hospital (greater than 3 days), convalescence (30 days) and the number of weeks of training in which remediation is required (0, 2, or 3). Sensitivity analyses were performed to evaluate the potential differences in both the absolute number of days lost in training and total cost of illness at 0, 14, and 21 days of remediation. The total lost time in training and cost of illness did not vary as much between 14 and 21 days as it did when considering 0 days remediation. The days lost and costs were much lower at 0 days. The overall assumption with regards to a recycle is that the trainee would not have to restart training completely and only make up the portions missed; therefore, a conservative 14 day estimate was used in the lost time in training due to recycle calculation.

Annual trends for overall SSTI rates observed among the active duty army recruit training population within this study are consistent with what has been observed in the current literature. Results from a military surveillance report evaluating bacterial skin

infections from 2000 through 2012 showed outpatient cellulitis rates among the Army active duty peaked from 2006-2008 and continually declined from 2009 through 2012.(13) This current study showed similar results with a peak in purulent SSTI rates in 2007 with a decrease in rates in 2009. Additionally, in this study, non-purulent rates experienced a steady increase from 2007 forward. This observation was similar to what was found in the December 2013 Medical Surveillance Monthly Report report.(13) Diagnosis codes were used in both of these studies to determine SSTI in this population. A potential does exist to report diagnosis codes erroneously; therefore, misclassifying cases. The alternative explanation is that "cellulitis and abscess" diagnoses are actually decreasing and folliculitis and non-abscess cellulitis infections are more commonly observed.

S.aureus SSTI annual rates among the recruit trainee population followed the same pattern as those observed among the overall active duty population from 2006 through 2009. This current study found rates peaked in 2008 and declined thereafter; a similar result was found in a study by Landrum et al.(114) Rates in the Landrum study peaked in 2008 with 525 *S.aureus* SSTI cases per 100,000 person-years to 380 cases per 100,000 person-years in 2010 (a 30% reduction); while this current study observed 151 cases per 100 training cycles in 2008 and 132 cases per 100 training cycles in 2009. Rates of MRSA SSTI in this study peaked in 2006 with 99 cases per 100 training cycles and declined to 87 cases per 100 training cycles in 2009. A similar trend was found in two studies of similar Army active duty populations.(118; 144) Authors found that CA-MRSA rates peaked in 2005 and then continually declined through 2010. Further exploration of trends beyond this current study's timeframe is warranted to examine if the

trends parallel or contradict what is found in similar studies with respect to overall, *S.aureus* and MRSA SSTI.

One trend that should be noted is that from 20006-2009 the absolute number and median bed days from "skin diseases" reported among the military recruit population as a whole in surveillance articles has not increased or decreased (around 10,000 and 3.5 days, respectively). Additionally, from 2006-2008, 25,000 days of limited duty were reported for "skin diseases" but dropped by over half to 10,000 days in 2009{AFHSC, 2010 #1108;AMSA, 2007 #63;AMSA, 2008 #64}. In this study, median lost time in training for overall SSTI remained the consistent across all four years of the study period. The absolute numbers of days for total lost-time in training and its specific elements decreased from 2006 through 2009, with 2009 having the least lost-time in training. Further evaluation is needed to determine if this trend remains or if it is different beyond 2009.

Another objective of this study was to identify potential predictors of lost-time in training and cost-of-illness in the trainee population using multivariate regression techniques. The factors that remained significantly different ($p<0.001$) in both overall, *S.aureus* and MRSA LTT and COI models related to type of disease, initial clinical care, and phase of training. Those trainees who had a MRSA SSTI or purulent SSTI had a greater amount of duty days lost and higher cost of illness than their respective counterparts (almost two times the days lost and cost). In fact, trainees with *S.aureus* or MRSA SSTI are twice as likely to be recycled from training or to have a hospitalization compared to those without such infections. Additionally, those that received an antibiotic with coverage for MRSA or had an I&D procedure also had significantly greater lost-

time in training and cost of illness. This observation is interesting in that reason would assume adequate initial care would lead to less time spent away from training and less costs. These factors could be potential indicators of more complicated or severe disease.

Lastly, trainees experiencing overall, *S.aureus* or MRSA SSTI during phase 1 of training had greater training days lost and a higher cost of illness compared with those trainees with an infection during the second phase of training. When phase 1 was evaluated in three week intervals, the greatest absolute number of cases occurred during weeks 4 through 6-a time of basic combat skills development, weapons qualification, and physical training. Furthermore, trainees with an infection during this time interval also were 50% and 28% more likely to have a recycle or hospitalization, respectively.

The results of the multivariate analysis prove useful in that they can direct the focus of future research and public health intervention efforts for prevention of overall, *S.aureus* and MRSA SSTI. First, such infections need to be prevented. These infections are occurring during a time in training in which the body is under a great deal of stress and factors such as physical training can compromise the skin integrity leading to an opportunity for infection. Considering most infections are occurring during weeks 4 through 6 of training, the trainees should be targeted during this time to improve and increase hygiene initiatives and increase awareness of infections.

Those trainees with SSTI overall who had an incision and drainage (I&D) procedure or received antibiotics for MRSA coverage had greater lost time in training and cost of illness (COI) than those without such care. Further evaluation showed that these same trainees were more likely to have a hospitalization, be recycled from training, or have a sick in quarters or work duty limitation disposition. In fact, for SSTI overall,

those who had an I&D were more three times more likely to have a recycle compared with those who did not have such a procedure. Additionally, a trainee with a MRSA-SSTI receiving an antibiotic with MRSA coverage is twice as likely to be hospitalized. Unfortunately, not all infections can be prevented, but receiving adequate initial care is important to prevent further complications (like hospitalizations) resulting in long periods of convalescence, limited duty time, and ultimately a recycle from training. Considering indirect costs contribute to 80% of the total costs, these infections need to be prevented or the trainee needs to receive prompt care upon first observation of the infection.

Strengths

Multiple factors make this study unique; the primary factors being, the population evaluated, the approach to estimating disease burden in this population, and the type of data systems used to derive estimates of burden. This study focused solely on the Army active-duty recruit trainee population over the course of four years. Previous reports have attempted to evaluate burden of overall SSTI among military service-members as a whole or provide limited information regarding the recruit training population, but have not fully explored the burden in this particular population. (14; 18; 114; 118; 203)

The methods by which burden was assessed are also novel, especially with regards to determining the recruit trainee's lost-time in training. This is the first known study that used such methods. This approach was used to assess lost-time in trying in order to provide a more accurate reflection of operational burden. Additionally, previous surveillance reports have shown the absolute numbers and rates of overall SSTI in the overall active duty military population, but rarely calculate the rates of MRSA SSTI. (8;

9; 114) Recent studies have attempted to associate clinical cultures with SSTI in order to estimate MRSA rates among trainees.(203)

This study also used multiple military health systems datasets to identify the recruit training population and their disease outcomes. These datasets provided comprehensive information so burden could be assessed at both a broad level and a more granular level (i.e. assess burden among sub-populations). Furthermore, existing military health system databases were used to calculate economic burden of overall and MRSA SSTI. These databases included individual-level costs data that allowed for a more robust assessment of both direct medical and indirect costs attributed to overall SSTI and MRSA SSTI in the Army recruit trainee population. A recent study by Lee et al aimed to calculate the costs of SSTI and community-acquired SSTI among the Army population. (120) They used simulation techniques to calculate their cost estimates and used probabilities from published studies (144) to calculate third-party and societal costs. The Lee study also attributes the costs to all Army installations, but it does not provide specific costs per installation nor does it evaluate these costs among the trainee specific population.

Because of the granularity of the data, analyses could be performed that evaluated both direct and indirect costs within different sub-groups that have not been evaluated previously, such as military occupational specialty, training installation, and rank. These groups are important because, if the economic burden is found to be higher in one group compared to another, resources can be better directed to the groups who are experiencing a large burden.

Previously published studies of economic burden of SSTI or MRSA SSTI focused on the economic burden within the inpatient healthcare setting as opposed to the outpatient, community setting.(9-11,18) This study is the first of its kind to solely focus on the Army recruit training population; a population known to be at high risk for SSTI and MRSA SSTI in which the clinical and economic burden is not well understood.(120) Again, this study can lead to further research with respect to cost of illness studies which has the potential to influence targeting of resources.

Another strength of this study is the use of modeling techniques to evaluate specific contributors to lost-time in training as well as cost of illness. Surveillance reports have attempted to estimate lost work time in this population(14) but little has been done to evaluate the factors associated with this burden. The same goes for COI studies. Only one study attempted to estimate the economic costs of community-aquired MRSA in the military population, but the authors did not perform multivariate anlayses to examine the predictors of these costs.(10)

Last, lost-time in training costs were shown to be an important contributor to the total costs of both overall SSTI and MRSA SSTI. The methodology used to calculate the total costs allowed for a more rigorous estimate to be calculated.(1; 34)Previous studies attempted to calculate lost-productivity costs (120) but they are not as readily apparent.

Limitations

This study is observational in nature so some limitations should be noted. Data were not collected in a prospective manner; therefore, systematic error could not be controlled. This study relied primarily on ICD-9-CM codes to identify SSTI. Although the diagnosis codes collected were based on methodology from previous studies, cases

could have been missed because of misclassification. Because data were pulled from a central system that obtains information from multiple training sites, the classification of SSTI could differ based on the specific training location. This same problem could also arise with respect to the clinical culture information that was obtained. We can be relatively certain, however, that MRSA-confirmed SSTI were in fact MRSA-confirmed SSTI as these cases were identified through clinical culture information.

Because culture rates were so low, evidence-based methods were used to derive conservative probable estimates of S.aureus and MRA SSTI. Assumptions to calculate these estimates were based on recent literature review, a prospective evaluation [IDCRP-055], and internal estimates [IDCRP-066]. Throughout the study, the confirmed and probable cases were combined in hopes to present a more accurate estimation of the disease, time and economic burden of S.aureus and MRSA SSTI. The assumptions used could have contributed to an overestimation of the burden which could have influenced the results of this study to lean toward an inflated burden. Both the effects of the confirmed and probable calculations were evaluated. Results showed that the use of confirmed S.aureus and MRSA cases alone actually skewed the medians toward more days lost in training and higher costs. Once the probable estimates were factored into the calculation, the opposite occurred, and the medians trended toward lower lost time in training days and cost of illness for S.aureus and MRSA. Including the probable cases likely improved the stability of the medians. Additionally, costs for hospital care could have been underestimated for this population because procedure information was not available for inpatient records. Procedures for further definitive testing were not identified and therefore were not factored into the costs. Moreover, information related to

complications from an SSTI was limited so it could not be included in calculating the hospital costs.

Time estimates such as time spent at a clinic visit, actual days of limited duty and sick in quarter, and recycled days were not available in the database. Conservative estimates and assumptions from previous studies were used to calculate the specific times. Therefore, estimates could have been over or underestimated which would ultimately influence the lost-time in training days and costs calculated. The only obtainable time estimate was hospital length of stay. A sensitivity analysis was performed with respect to the "recycled" population and results showed that the number of days for recycle does affect both the lost time in training burden and the cost of illness if the number of days for recycle is less than 14 days of remedial training. If less than 14 days, the recycled population falls third to work duty limitations as the top contributor to both lost time in training and cost of illness. One should consider though, that this study assumes that a trainee must remediate at least a portion of his or her training. Setting the number of remediation days to 0 would be erroneous and would underestimate the time and cost burden associated with SSTI overall as well as S.aureus and MRSA SSTI.

Public and military health implications

This study shows the importance of overall, *S.aureus* and MRSA SSTI beyond the inpatient health care setting. Although the incidence of these infections seems relatively low within the training population, the direct and indirect costs attributable are substantial. A need exists to look beyond the inpatient care setting and focus potential efforts toward overall, *S.aureus* and MRSA SSTI prevention in the ambulatory care arena. It can be said with certainty that more work needs to be directed at reducing not

only the epidemiological burden but the economic burden of these infections as well. Indirect costs comprised the majority of total cost of illness. These indirect costs include not only time spent receiving care but time spent away from work in order to convalesce or repeat specific portions of training. Ultimately, it would be beneficial to prevent all infections occurring. A need exists to prevent the infection getting to the point in which an individual requires hospitalization, limiting the need to prescribe limited work time and further convalescence.

Understanding the burden of overall and MRSA SSTI in the recruit training population is important. In an era of limited resources, sound analyses of disease burden and its impact in this population as a whole as well as sub-populations can drive the population at which the prevention strategies are aimed. The impact of disease in terms of monetary resources used can also inform potential prevention programs.

The largest contributor both in terms of time and money was lost productivity. Lost productivity was measured by lost-time in training days which encompassed time spent away for medical care and convalescence as well as being "recycled" from training. Final analyses showed that being recycled is a major factor with respect to lost productivity as it led to over a quarter of the days lost in training and 25% of the total costs. This is significant as only 1.7% of the trainees with an SSTI experienced a "recycle". In terms of training, this also means that a space is being lost for each person that needs to recycle into a new training cycle. In terms of healthcare, this means that this population is consuming multiple medical resources before being recycled. The aim should be to prevent a recycle from occurring because of overall and MRSA SSTI.

CONCLUSIONS

Lost time in training is a valuable estimate of both epidemiological and economic burden. Other studies have used a similar measure (such as absenteeism in schools) to evaluate the impact of infection on productivity. Using the lost-time in training estimate allowed for determining which specific element contributes the most to overall and MRSA SSTI burden. It was found that the "recycled" population has a significant role in burden and resources can be directed toward this population. The lost-time in training metric can be included in future studies of burden beyond the military training population to pinpoint the specific areas where productivity losses occur.

This initial study lays the foundation for future studies of overall, *S.aureus and* MRSA SSTI burden. Future research efforts should possibly expand the time-frame of this current study to evaluate further trends as well as the study population. MRSA SSTI has been known to be pervasive in similar populations (9; 146; 203). Understanding the burden in terms of lost-time in training would again be helpful in directing resources. Further analyses could answer questions as to whether the lost-time in training burden is the same, more or less across all services.

This study found that significant overall SSTI and MRSA SSTI burden exists in the Army active duty recruit trainee population. Further research should be pursued to explore this lost time metric not only in the active duty trainee population but other similar groups as well. This study has important significance as it is the first study to evaluate the costs of SSTI and MRSA SSTI among the Army active duty recruit trainee population using a cost of illness framework. The estimates attained from this analysis will be used in developing a decision analytic model to assess the cost-effectiveness of a

personal-hygiene based prevention strategy against overall, *S.aureus* and MRSA SSTI in an active duty military trainee population.

In summary, more efforts need to be directed toward prevention of these infections from occurring within this population, specifically infections with *S.aureus* and MRSA involvement. As was observed in the results, median lost time in training and cost of illness were twice that of those without such infections. Results from this study indicate that much of the costs are related to time spent away for care and the need to convalesce from *S.aureus* and MRSA SSTI. Policies should be implemented to identify these infections promptly to reduce the need to hospitalize or treat in such a way that requires extensive convalescence or a need to remediate training. Ultimately, the goal should be to prevent all infections from occurring; thus far, prevention efforts have not led to control of this military public health burden.(65; 213) More effective prevention strategies such as vaccine development could effectively reduce this burden, but further research needs to be carried out. Until this time, more can be done to identify target populations at risk for these infections and give them access to materials to improve hygiene and awareness as well as access to prompt initial care.

Chapter 4 Cost effectiveness analyses of hygiene strategies to prevent methicillin resistant *Staphylococcus aureus* associated skin and soft tissue infections

INTRODUCTION

Scant cost-effectiveness literature exists on hygiene practices to prevent skin and soft tissue infections (SSTI) or methicillin-resistant Staphylococcus aureus (MRSA)-associated SSTI in the community population. (172) No previous literature exists regarding cost-effectiveness of strategies to prevent SSTI and MRSA-associated SSTI in the active duty military population, specifically the trainee population. Evaluations of the cost-effectiveness of MRSA prevention strategies have generally been limited to the hospital setting. Uncertainties remain regarding costs and effects associated with a community-wide program that includes simultaneous implementation of multiple hygiene-based measures on infection rates. Cost-effectiveness of such a program has yet to be determined in a prospective fashion; therefore, further assessment is warranted.

FRAMEWORK

This cost-effectiveness analysis (CEA) used decision analytic (DA) methodology to assess the incremental costs and effects of hygiene-based approaches to prevent SSTI and MRSA-associated SSTI in the active duty military training population. DA frameworks have been used in multiple cost-effectiveness studies regarding MRSA empiric therapy and infection control measures.(56; 119) Such a model is best suited to evaluate interventions to prevent or treat illness of a short duration like an acute infectious disease. A decision analysis model calculates the costs and effects associated with an event in the event pathway. Additionally, DA models have been both used to simulate clinical outcomes and costs based on evidence-based literature reviews and prospective cohort data.(36; 150)

This study sought to evaluate the cost-effectiveness of an enhanced multi-component hygiene-based intervention for SSTI prevention among active duty Army trainees. This objective was composed of two parts. First, cost-effectiveness estimates were derived using evidenced based information from a retrospective study using pre-existing military health system data and a systematic review of the literature (SSTI Burden Protocol **[IDCRP-066]**). Probability, cost, and effect information obtained from this analysis served two functions (1) model simulation and provision of base case estimates. Second, information obtained from Fort Benning trial **[IDCRP-055]** was used to build a model based on real world, prospective data. Average and incremental cost-effectiveness ratios were generated to evaluate the overall costs and effects of hygiene strategies in this population. Ultimately, the cost-effectiveness of each component of the hygiene strategy was compared.

Cost effectiveness was also evaluated based on estimates derived from a systematic review and meta-analysis of the literature. These estimates gave a broad sense of the cost and effects of hand hygiene and personal hygiene programs as well as the use of chlorhexidine to prevent skin and soft tissue infections in congregate community settings. This information provided a base case by which to compare a prospective cluster randomized control trial of hygiene strategies in a similar setting.

DATA AND METHODS

Model overview and analytic horizon

The DA models were developed and based on the care and treatment pathway an individual would follow upon developing an infection (**figure 33**). The decision node was the type of hygiene strategy the trainee received. The decision pathway included several

chance nodes related to the probabilities of developing an infection and identifying the type of infection. For each hygiene strategy, a person that developed an infection followed either the purulent or non-purulent infection pathway. Ultimately, at the terminal node for each pathway, the individual's infection either resolved or complicated. A trainee with a resolved infection is one that does not require any further treatment. A complication occurred when the trainee was hospitalized or extended hospitalization (±4 days) leading to required remedial training. Cost and effects were determined for each pathway.

The time horizon was one training cycle (105 days). A short-term time horizon was considered in this model for two reasons. Training lasts on average 14 weeks±1 week and SSTI are normally acute infections. The hygiene strategy is only provided during training and not beyond. Furthermore, SSTI can recur, but the focus of the study is to evaluate the ability of the hygiene strategy to prevent infections during the training period. If a trainee has a recurrent infection, it is likely to occur while in training.

Population at risk and setting

Military trainees are known to be at high-risk for skin and soft tissue infections (SSTI) such as abscess and cellulitis, and a significant proportion of these infections are caused by *Staphylococcus aureus* organism. (9; 13; 40; 216) Outbreaks of MRSA-associated SSTI have been well described in military settings but less is known about the burden of these infections on the military healthcare system. (8; 9; 28; 51) Disproportionately higher rates of overall and MRSA-associated SSTIs among military training populations can result in an increased health care burden and impairment in the ability of soldiers to participate in and successfully complete training programs. For the

purposes of this analysis, trainees attending One Stop Unit Training (OSUT) at Fort Benning, Georgia were included in the study. Trainees were male and their ages ranged from 17-42 years of age. OSUT lasts on average 14 weeks and is split into two phases. Phase 1 lasts 9 weeks and Phase 2 lasts 5 weeks. Information regarding the study population has been reported elsewhere.(65)

Hygiene strategies

Hygiene strategies from the Fort Benning Study [FBS (IDCRP-055)]

Three hygiene strategies were evaluated during a prospective, cluster randomized trial conducted at Fort Benning Georgia. The strategies have been reported in detail elsewhere. (65) In summary, the three strategies were the standard group (SG) the enhanced standard group (ESG) and the chlorhexidine group (CHG). Trainees within the SG only received a personal hygiene briefing at the beginning of training and standard care upon developing an SSTI. ESG received the same information and treatment as trainees within the SG but were also instructed to take a weekly 10-minute shower with soap and water along with additional supplemental education. Trainees in the CHG were offered chlorhexidine body wash as well as the components of SG and ESG.(65)

Hygiene strategies from the systematic review of the literature (SR)

In addition to the strategies evaluated from the FBS (IDCRP-055) (65), evidenced –based hygiene practices were evaluated through a systematic review of the literature. These practices occurred within the community and included components such as hand and personal hygiene, community-based hygiene education, and environmental disinfection. For the purposes of this CEA, evidenced based-strategies were categorized

into three categories chlorhexidine component with hygiene education, hand hygiene promotion, and standard practice.

Standard practice

Standard practice included basic treatment and care of an individual who developed a SSTI or MRSA SSTI. Existing measures include incision and drainage, wound care, follow-up visits, antibiotic treatment and if necessary, and hospitalization.

Probability estimates

Multiple probabilities were calculated for the treatment pathway in the DA model. These probabilities include the development of an infection, purulent infection, clinical culture, culture positive for *S.aureus,* and *S.aureus* resistance towards methicillin as well as infection resolution or complication

Costs

Hygiene strategy program costs and timeframe

Hygiene strategy costs were calculated over the time spent in training from entry until departure. Trainees within the Standard Group (SG) received a medical briefing and standard care. The medical briefing had no costs associated with it. Trainees in the enhanced standard group (ESG) received one first aid kit during their time in training at the cost of $1.46. Trainees within the Chlorhexidine group (CHG) received the first aid kit and a bottle of chlorhexidine body wash (4% chlorhexidine gluconate, Hibiclens, Monlycke Health care, Norcross, Georgia) which cost $5.24 per trainee. Over the entire study period, there were approximately 10,000 trainees per group. Total cost of hygiene

strategies were $15.9K and $52.6K for the ESG and CHG, respectively (or $168 and $556 per training cycle, respectively).(65)

Standard practice costs

Standard practice costs were generated using military health system data sets and methods used by the Army Health Hazards Assessment Program. Total costs included both direct medical costs (DMC) and indirect costs (IDC). DMC were calculated as the sum of clinical outpatient, ER and hospital care costs; while IDC were calculated as the product of training costs per day and the sum of days lost because of time away from training. The calculations for these costs have been reported elsewhere. Please see **appendix G** for more information. Cost information was not collected in a prospective manner. Instead, for each SSTI case an average cost estimates for each type of care was applied to the prospective dataset to calculate the costs associated with standard care received during training.

Effectiveness measures

Using the military health care system prospective in a training setting, lost-time in training was used as the effect estimate. Lost-time in training was calculated as the amount of time spent away from training in order to receive care during a medical encounter (i.e., clinic, ER, or hospital visit) as well as being assigned to limited duty or 'sick in quarters' status, or training remediation. Estimates were derived using methods from the Army Health Hazards Assessment Program. Information was obtained from a prospective study to calculate the number of training days lost from limited duty, quarter's assignment, and hospitalization. Multiple assumptions were made to generate clinic visit and remedial training LTT estimates. In brief, time spent away from a clinic

visit was equivalent to half a day. Follow-up visits received the same amount of time. Those spending greater than 4 days in the hospital were assumed to remediate training. For those who remediated training it is assumed that they would receive 30 days of convalescence plus 14 days to repeat the section of training that was missed during the trainee's recuperation period. Assumptions for lost time can be found in **Appendix F**.

Outcome measures

The costs averted from the use of hygiene strategy (S, ES, or CH) were calculated. Costs averted were equivalent to the difference between the total COI associated with standard practices and the total costs of the hygiene strategy as well as cost of care for an infection that developed while using the strategy. Costs averted were annualized. As with costs, lost-time in training (LTT) days averted were also calculated. The number of days averted is equivalent to the difference between LTT for standard practice and LTT associated with an infection that developed while using a specified hygiene strategy. LTT averted was also annualized.

Marginal cost effectiveness ratios were calculated for each of the strategies in each of the models. General calculations are provided in **Appendix K**. These calculations were derived from Gold, Brown and Bounthavong. (30; 36; 77) Costs estimates were generated from the FBS [IDCRP-055] and IDCRP-066. Effectiveness estimates were obtained from the FBS [IDCRP-055], IDCRP-066, and a systematic review of the literature.

Incremental cost effectiveness ratios (ICER) were calculated for each of the strategies in each of the models developed. Example calculations provided by Gold, Brown, and Bounthavong are provided in **Appendix K**. This ratio is generated to assess

the additional cost per infection avoided compared to the next effective strategy.(30) Costs estimates were generated from the FB MRSA study [IDCRP-055] (65) and the SSTI Burden Protocol [IDCRP-066]. Effectiveness estimates were obtained from FB MRSA study [IDCRP-055] (65) and a systematic review of the literature.

Cost-effectiveness Analysis

All analyses were performed using Tree Age Pro Suite Software, version 14.0. The analysis pathway is outlined in **figure 34**. Specifically, three analyses were performed- primary, secondary, and sensitivity analyses. The below paragraphs provide further details regarding each analysis.

Primary analysis

The primary analysis involved the evaluation of prospective data obtained from the FBS (IDCRP-055) compared to estimates from BOI (IDCRP-066).(65) Total cost and LTT days averted were calculated for each hygiene strategy (S, ES, and CH). Both marginal CER and ICER were calculated for each hygiene strategy to evaluate which strategy was most cost-effective.

Secondary analyses

Secondary analyses were performed using similar methods from the primary analysis. These analyses were conducted to compare costs and effects by training location (Fort Benning, GA only), phase of training and the season of training. Previous results showed that infection rates varied for trainees depending on the phase of training as well as the season in which the infection occurred. (65)

Sensitivity analyses

Probabilistic sensitivity analysis using Monte Carlo simulation was also performed to evaluate uncertainty around study parameters. All parameters related to probabilities, costs, and effects included in the analysis followed triangle distribution (low, medium, and high). Probabilities included the proportions of the population with overall and MRSA SSTI culture, or hospitalization within one of the three intervention groups. Estimated cost averted and effect estimates (LTT averted and risk ratios) were obtained from a systematic review of the literature as well as FBS (IDCRP-055). (85; 172) Total costs included the sum of the cost of standard practice and the specified hygiene strategy. Costs averted were equivalent to the difference in costs between the standard practice and a hygiene strategy. LTT averted was equivalent to the difference in days lost between the standard group and a hygiene strategy. For each simulation, 1000 samples were taken.(149)

RESULTS

Primary analysis

Overall and annual SST incidence over a four year period (2006-2009) among all OSUT sites was around 8%. Of these infections, 62% were purulent. Approximately 34 percent of purulent infections had cultures obtained during this time. *S.aureus* isolates accounted for 85% percent of the cultures and 65% of these isolates were resistant toward methicillin. Complications from infection occurred about 4% of the time.

As previously mentioned, three hygiene strategies were prospectively evaluated at Fort Benning, Georgia- Standard (S), Enhanced Standard (ES), and Chlorhexidine (CH). A total of 1203 SSTI overall and 316 unique MRSA SSTI occurred during the study period. Probability of developing a skin and soft tissue infection (SSTI) ranged from 3% (SG) and 5% (CHG). Of those that developed an SSTI, more than half were purulent SSTI. Culture rates among the purulent SSTI ranged from 49% to 61%. Between 83 and 87 percent of the clinical cultures tested positive for *Staphylococcus aureus*. The proportion of *S.aureus* isolates resistant towards methicillin was lowest in the chlorhexidine group (49%) compared with 60% and 65% among ES and S groups. Hospitalization occurred most often in the standard group. Persons remediated training less often in the chlorhexidine group. The probability of overall and MRSA SSTI occurred most often in the summer during phase 1 of training.(65) (**Table 24**)

Each person that developed an infection follows a standard care pathway; therefore, costs for standard care were calculated for each recipient of care. The annual total cost of care without intervention was 12.9 million USD (estimate obtained from IDCRP-066), across all OSUT sites. (**Table 24**) Total annual costs for standard care among trainees with an infection within the SG were $402.6K. Total annual cost of the

hygiene strategies was $602.4K (ESG) and $575.2K (CHG). These costs included the specific hygiene strategy costs. Average costs per trainee for each group were $1,259(IQR: $2,040); min: $417 max: $38,038] (SG); $1,255 (2182); min=417, max=38,456 (ESG) and [$1259 (1926); min=417; max=41849.45 (CHG). Additionally, within the total costs for the end of each pathway, the cost of the specific hygiene strategy was factored into the equation. ESG costs for the entire study period among all who developed an infection was $639.48. Cost of CHG for all of those who developed an infection was $2420.25 (**Data not shown**).

Approximately 18,000 days were lost in training annually across all OSUT sites (Table 1). Overall, total lost time in training equated to 3,660 days during the prospective trial's two year study period (mean=3.05±5.26; median=1.9[0.5-3.5]). (**Table 24**) Almost 80% of these days lost in training were associated with clinic visits and work duty limitations. When comparing hygiene strategy groups, ESG experienced the most days lost in training 1,435(3.28±5.88), SG and CHG lost 860 and 1364 days, respectively. Like with the overall total, most time was lost due to clinic visits and work duty limitations across all strategies. With respect to lost time due to hospital visits, those in the standard group experienced more absolute days lost in training (28) compared to the ESG (14) and CHG (22). The CHG and ESG experienced 2 to 3 times the absolute days of remedial training compared to the SG (**data not shown**).

Total cost averted and LTT averted were calculated. On average, $118.8, K, 116.9K, and $117.2K was averted annually per training cycle for S, ES, and CH groups respectively. Additionally, use of S, ES, and CH averted 167.7, 164.8, and 165.3 days (respectively) annually per training cycle (**Table 24**).

Marginal cost effectiveness ratios (CER) were $661.7, $662.3, and $663.8 for S, ES and CH groups, respectively. Overall, use of the chlorhexidine strategy averted more costs ($1440.80) and lost time in training days (2.17) compared with the standard and enhanced standard groups (**Table 25**). Incremental cost effectiveness ratios (ICER) showed $665.8 was averted for each additional day lost in training averted when using the ES methods compared to S methods. An extra $671.1 was averted for each additional day lost in training averted when receiving Methods compared to using the standard strategy. Lastly an extra $665.8 was averted for each additional lost time in training day averted when using chlorhexidine compared to the enhanced standard group. (**Table 25**)

Secondary analysis

Secondary analyses were conducted to evaluate the effect of training location (Fort Benning, GA) and temporal factors (phase of training and season) on cost and effect outcomes. Results are shown in the following paragraphs.

Training location

Probabilities

At Fort Benning, GA, probabilities were calculated to assess the baseline before hygiene strategies were implemented. These probabilities were generated from IDCRP-066. Without implementation of hygiene measures, 6134 (9.6 %) of the Fort Benning trainees (64,226) developed an SSTI over a four year study period (2006-2009) - 2887 (4.5%) developed a MRSA SSTI. Of those that developed an SSTI, 262 (4.3%) developed a complication. **(Table 26)**

Costs

Annual standard practice costs for SSTI overall totaled approximately $3.2 million USD per year at Fort Benning from 2006-2009. Total annual cost of a MRSA SSTI was about $499K USD per year. A complicated MRSA SSTI costs approximately $313K USD annually. Average costs of a MRSA SSTI that resolved were estimated at $2500 USD per trainee; while a complicated case cost approximately $15.6K USD. **(Table 26)**

Effects

On average, trainees at Fort Benning with an SSTI lost 4,500 days in training annually overall, 3041 days were lost in training for a MRSA SSTI that resolved and 1629 days were lost for a complicated MRSA SSTI. Annually, this equated to about 760 and 407 days for resolved and complicated MRSA SSTI, respectively. Approximately, 3.8 days were lost per trainee with a MRSA infection that resolved while a trainee with a complicated MRSA SSTI lost 20.4 days. **(Table 26)**

CER and ICER

Each hygiene strategy (S, ES, and CH) was compared with the baseline, standard practice estimates at Fort Benning, GA to generate CER and ICER. Results revealed greater cost-effectiveness within the ES group compared with the S and CH groups. ES averted slightly greater costs per training cycle when compared with S and CH ($64.71, $59.46, and $58.61, respectively). Additionally, the differences in the amount of LTT (days) averted per training cycle between all three groups were minimal (0.09, 0.09, and 0.08, LTT (days) averted, respectively). (**Table 27**) Overall, marginal CER were greater in the CHG compared with S and ES groups (760.45, 658.14, and 682.39, respectively.).

A total of $1171.51and 610 was averted for each additional LTT day averted within the ESG compared with the S and CH groups. (**Table 27**)

Phase and season of training

Probabilities

The proportion of SSTI, culture, *S.aureus,* MRSA, and complication occurring in each intervention group were calculated for each chance node of the decision tree and evaluated by phase and season of training. During phase 1 of training, the proportion of those trainees with a purulent SSTI (58%), MRSA SSTI (46%), and complicated MRSA SSTI (0.9%) was lower in the chlorhexidine group compared with the standard (55%, 59%, and 0.12%) and enhanced standard (66%, 57%, and 0.08%) groups. Additionally, during phase 2 of training, the proportion of those with purulent SSTI (40%), culture (90%), MRSA SSTI (48%), and other organism with a complicated infection (0%) was lower in the chlorhexidine group compared with the other two strategy groups (S:61%,68%, 1.6%, and 1.6%; ES: 67%, 81%, 1.2%).

Furthermore, the proportion of SSTI was highest for the chlorhexidine group (79.2%) during the fall/winter seasons during phase 1 of training; while the standard and enhanced standard groups experienced a greater proportion of SSTI during spring/summer months during phase 1 of training (80.4% and 88.4%, respectively). MRSA SSTI occurred most often during the spring/summer months in phase 2 of training for chlorhexidine groups (65.4%) unlike the enhanced standard group where cases occurred more often during the fall/winter months of training phase 2 (73%).

Costs

Total costs were explored by phase of training and season in which the infection occurred. Overall, highest costs for all strategies were experienced spring and summer months during phase 1 of training- they were 3-8 times greater when comparing phase 1 to phase 2. Total costs were 2-3 times greater in the fall/winter months when comparing phase 1 to phase 2 among all groups. SG and ESG experienced the least costs during phase 2 of the spring/summer season compared to the CHG which experienced least costs during the fall/winter during phase 2 (data not shown).

Effects

Lost time in training was also evaluated by phase and season of training in which the infection occurred. Like with costs, most lost time occurred among all strategies in spring/summer season during phase 1 in training. About 4-5 times more days were lost during this time compared to same season during phase 2 (data not shown).

CERs and ICERS

During phase 1 of training, those within the CH group averted more costs ($758.9 USD) and LTT (1.17 days) per training cycle compared to those who used the S and ES strategies (figure 3). No considerable variation was found between the hygiene strategies in regards to the marginal CER and ICERs. (**Figure 35**) Conversely, during phase 2 ES outperformed the S and CH groups by averting more costs ($294.89) and LTT (0.43 days) per training cycle. Marginal CER were greater for the ES group ($693.69/LTT) compared to S and CH strategies ($676/LTT and $674.95/LTT). ICERs revealed greater cost-effectiveness of ES over S and CH groups. The CH group was more cost effective that the S group (**figure 35**).

Evaluation of strategies by phase and season of training showed that most of the costs and LTT days were averted during the spring/summer months in phase 1 of training across all strategies (**figure 35-36**). Costs averted ranged from a low of $321.90 USD per training cycle in the standard group and a high of $494.49 USD per training cycle in the ES group. LTT averted ranged from 0.49 (SG) to 0.76 (ESG) days per training cycle. Marginal CER did not vary substantially between the groups across phase and season. ICERs revealed that the chlorhexidine strategy is cost-effective during phase 1 in the fall/winter months as well as during phase 2 in the spring/summer months compared to the other two strategies (**figure 36**). The chlorhexidine strategy is only cost effective over the standard strategy during phase 1 in the spring/summer months. The ES strategy, on the other hand, is more cost-effective during phase 1 in the spring/summer months and phase 2 in the fall/winter months when compared with the standard strategy (**Figure 36**).

Sensitivity analysis

Probabilities

Probabilities were derived from a systematic review and meta-analysis of the literature. Results of this study have been reported elsewhere. Probability estimates were derived for incidence of SSTI and MRSA as well as the proportion of those infections which had a culture or hospitalization (**Table 28**). Estimates from the systematic review were designated to three primary categories (1) standard practice (2) Hand Hygiene Promotion (HHP) and (3) Chlorhexidine (CH) group. Results showed that across all categories, the proportion of those receiving one of the three interventions who developed an SSTI overall and MRSA SSTI ranged from a 4-30 % (S), 4-12% (HHP) and 4-23% (CH). Incidence for overall and MRSA SSTI was highest in the standard practice (30.4%)

and HHP (11.5%) groups, respectively. Culture rates ranged from a high of 88.7% in the Hand Hygiene Promotion group to a low of 4% in the standard practice group. The proportion of individuals with an infection hospitalized ranged from a low of 1% in the Chlorhexidine group to a high of 36% in the standard practice group.

Costs

The cost of standard practice for a MRSA SSTI was estimated by Sander to range from $400-1000. Additionally, in the same study, the total cost of a hygiene strategy that included Chlorhexidine was $850. Another study found that the total cost for a hand hygiene program was $775. Unadjusted total costs of SSTI overall were highest in the SP group (1.43 million USD) and lowest in the HHP group (542 thousand USD). The chlorhexidine group experienced the lowest total costs associated with MRSA SSTI (433 thousand USD). The highest costs for a complicated infection were observed in the SP group (435 thousand USD). Unadjusted costs averted were also calculated for the HHP and CH groups. On average more cost were averted in the HHP group compared with the C group for a resolved SSTI ($2866 and $941, respectively). Conversely, for complicated SSTI, resolved MRSA SSTI, and complicated MRSA SSTI more costs were averted within the CH group compared with the HHP Group (**figure 37**).

Effects

The number of days lost in training was calculated for each group. On average, those within the standard group lost more time overall compared with the HHP and CH groups, with one exception. Those in the HHP group with a resolved MRSA SSTI experienced more lost time in training compared with the SP and CH group (3558, 2801, and 2168 days, respectively).

Relative risks. Like with total costs, those in the CH group with a complicated SSTI, resolved MRSA SSTI, and complicated SSTI, averted more LTT compared to those in the HHP group.

CERs and ICERS

Multiple factors influenced the model to include the probability of an infection being culture positive for MRSA as well as the probability of a person with a MRSA infection being hospitalized. Baseline estimates, prior to sensitivity analysis, showed that compared to the chlorhexidine strategy, the HHP strategy averted greater costs on average per training cycle among persons with SSTI $2476 vs 6988 USD) (Figure 5). Chlorhexidine was substantially averted more costs and days lost in training compared to the HHP among persons with a resolved MRSA SSTI. (Figure 5) Chlorhexidine averted $1647.30 USD and 8.96 days lost in training compared with the HHP strategy which did not avert costs or LTT (Figure 5). Among those with a complicated MRSA SSTI, the HHP strategy averted slightly more costs ($3905 vs $3598 USD), but the CH strategy averted a greater amount of days lost in training (47 vs 8 days).

Monte Carlo probabilistic sensitivity analysis was used to estimate the marginal cost effectiveness ratios (CER) and incremental cost effectiveness ratios (ICER). These estimates were evaluated and compared among the HHP and CH groups. Results showed that almost three times the costs (USD) and LTT (days) were averted on average in the HHP group compared to the CH group among those with an SSTI overall. Conversely, when evaluating MRSA SSTI specifically, chlorhexidine strategies averted more costs and lost days in training compared to the HHP strategy (figures 38-39).

DISCUSSION

This study sought to calculate cost effectiveness ratios and determine the incremental cost effectiveness ratios of hygiene strategies aimed toward prevention of SSTI overall and MRSA SSTI. Previously, cost-effectiveness analysis related to methicillin-resistant *Staphylococcus aureus* associated SSTI literature has been limited to studies regarding antibiotic treatment, surveillance, and infection control measures among hospitalized populations. (36; 56; 119; 150) Until now, uncertainty existed about the cost effectiveness of MRSA SSTI prevention programs involving hygiene strategies in the community setting. Only one study attempted to assess the cost effectiveness of a hygiene promotion program among college athletes.(172) Within the military training population, multiple hygiene strategies have been implemented to prevent SSTI and MRSA associated SSTI, but the costs of these programs were not well understood and the effects of these programs varied from effective to ineffective. (65; 146; 176)

Considering the paucity of CEA literature available, there is little by which to compare the results from this current study in terms of costs and effects. Only one previous study concluded that implementation of a program that included hygiene promotion elements as well as chlorhexidine showers could be cost-effective among college athletes.(172) Authors found that the total cost of such a program for one college was $850 as opposed to a cost of one infection could range from $400 to $1000. The program saved the college between $4,000 and $10,000 per year (about one-quarter of the costs from the previous three years). In comparison, in the military training environment, standard medical practice costs approximately $2500 per MRSA SSTI. A hygiene strategy including education and chlorhexidine components costs $5.25 per trainee. Based on estimates generated from a previous retrospective study, approximately

240 trainees per year at Fort Benning developed a MRSA SSTI when only standard care was implemented, which costs an estimated $600,000 in direct medical care and indirect costs. During a prospective trial at Fort Benning from, 95 MRSA SSTI occurred among those receiving a hygiene strategy with education and chlorhexidine. With hygiene strategy and standard care costs combined for each case the total costs were approximately $400,000- saving about $200,000 each year. A hygiene program for military trainees would be implemented on a greater scale, but could reduce the burden on the medical system in terms of the amount of medical resources uses.

One interesting finding in this study is the difference in cost-effectiveness between the chlorhexidine and enhanced standard strategies. Inspection of the costs and lost time in training days averted were greater for the chlorhexidine strategy compared to the enhanced standard and standard strategies. Further analysis revealed that incrementally, more days and costs averted was associated with the chlorhexidine strategy compared to the enhanced standard and standard groups. The proportions of purulence, culture, and MRSA SSTI were consistently greater along the decision analytic pathway for the enhanced standard group compared to the chlorhexidine group. Smaller proportions generate greater costs averted. Additionally, along the infection pathway, the number of days lost in training averted was greater in the chlorhexidine group with respect to resolved MRSA SSTI and SSTI cultured positive for “other” organism as well as a complicated MSSA SSTI compared to the enhanced standard group. Differences in costs and effects were also observed along the decision pathway when comparing the chlorhexidine group and standard group. The probability of developing a complication within these categories of the pathway was more likely within the standard group

compared to the chlorhexidine group-which contributed to slightly greater costs and lost time in training averted in this group. The rationale for these results could be explained by the way that chlorhexidine works against the MRSA organism as a decolonizing agent. Additionally, those individuals with complicated infections may require an additional hygiene protocol in conjunction with standard care that was not available during the trial.

Recommendations for future research or implementation of hygiene strategies

This cost-effectiveness analysis included probability and lost time in training estimates from a prospective trial. Additionally, total and average costs for standard care were calculated based on information from a retrospective analysis of burden data. Future prospective trials should include cost components within the data collection strategy. Gathering such data could generate more precise estimates which would allow for a more robust reflection of cost effectiveness of a hygiene strategy. Although retrospective data were used to calculate costs, it should be noted that all cost data retrieved were from a military health system database. The cost estimates provided were already discounted and factored all costs related to a medical visit for SSTI and MRSA SSTI (i.e., office visit, laboratory procedures, and pharmaceutical costs). These cost estimates mirror the direct medical care costs associated with SSTI and MRSA within the military health system.

Because the prospective trial occurred at Fort Benning, Georgia, the majority of the analyses were restricted to Army Infantry Trainees attending One Stop Unit Training at Fort Benning, Georgia. Epidemiologic and economic burden of SSTI and MRSA SSTI exists among other OSUT training sites (i.e. Fort Jackson, SC). Additionally, this burden is not limited to solely Army trainees; the burden also exists among the other services.

Future cost-effectiveness analysis should be expanded to elucidate the cost-effectiveness of these strategies among other military populations. Results of cost-effectiveness could vary from site to site. Hygiene strategies deemed cost-effective within one training location may not be cost-effective at another. Performing such analysis can direct resources and target populations that could benefit most from hygiene strategies.

Results from secondary analyses showed that CERs and ICERs for hygiene strategies varied by the phase and season of training in which an infection occurred. Such a result is not unexpected as rates of SSTI and MRSA SSTI are influenced by these temporal factors; therefore, this influence could extend to costs and lost time in training. The enhanced standard proved to be cost-effective over standard practice during spring/summer phase 1 and fall/winter phase 1. Conversely, the chlorhexidine group was cost-effective over stand practice only during phase 1 and spring/summer phase 2. The information derived from this secondary analysis can be used to project which strategy would be best suited for implementation during a specific time period. Implementation of the chlorhexidine strategy may only be necessary during spring and summer months and phase 1 of training; while the enhanced standard could be used during fall/winter months during the first phase of training. Currently at one military training facility, recruit trainees receive a hygiene strategy that includes showers with chlorhexidine. (146; 196) Every trainee who enters training must use this hygiene approach when entering training and then multiple times throughout the course of training. The results from this current study could be used to inform such a policy and potentially provide further direction as to whom and when these methods should be implemented.

Strengths

Multiple factors make this study strong. The primary factor being that most estimates were generated from a cluster-randomized clinical trial (IDCRP-055) that examined the effects of hygiene strategies on SSTI overall and MRSA SSTI within a military training population.(65) This study provided granular level data by which to calculate cost and lost time in training estimates for each trainee participating in the study who developed an SSTI. The effects in terms of rates and relative risks were calculated in a prospective fashion.

The cost estimates that were derived came from military health system databases. Additionally, not only were direct medical care costs included in the total cost estimates, but indirect costs were also calculated. With respect to this analysis, on average, direct medical costs contribute to only 12% of the total costs for a MRSA SSTI ($2500). Indirect costs within this analysis included time spent away for clinic and hospital visits as well as recuperation and remedial training. These costs often are not accounted for within cost effectiveness analyses because the data are limited to the data collection parameters of the study. Before the prospective trial commenced, variables pertaining to lost-time away from training were developed for the data collection tool.

Lost time in training as an effect estimate has its benefits. Studies evaluating the effect of hygiene strategies on SSTI overall and MRSA SSTI often use relative risks or similar ratios to determine the impact of the intervention. A non-clinical endpoint such as days lost could be more informative to policymakers from the military perspective. Operationalizing cost-effectiveness of an intervention in terms of days can assist the policy maker in visualizing the impact of the intervention as opposed to an estimate such as a relative risk.

Limitations

This study does have its limitations. The model assumptions used to estimate indirect costs and lost-time in training days could have been over or underestimated. Indirect cost estimates are influenced by the number of days lost in training. As the days lost in training increase so do the costs. This is attributed to the fact that indirect cost is equivalent to the product of number of days lost in training and the average salary for a trainee. Although, the estimates for length of stay in the hospital, work duty limitations, and sick in quarters are relatively certain as these estimates were collected during the prospective trial, less certainty exists around the time estimates for a clinical visit and remedial training. In the **IDCRP-066** study, sensitivity analyses were performed to evaluate the effects of the number of days lost from remedial training on cost and time. After performing the sensitivity analysis, it was agreed that a conservative approach would be used to estimate time for remedial training as to not overestimate the cost and time for this factor.

Another limitation exists with respect to the relative risk estimates generated from systematic review and meta-analysis. The meta-analysis showed significant heterogeneity around the effect estimates; therefore, a pooled effect could not be used. The estimates used in this study came from published literature regarding the use of chlorhexidine, but the studies were limited in that many were case-control studies and often interventions were implemented reactively rather than proactively.

Last, the prospective trial generated effect estimates that showed that significant reductions in rates were not observed with the implementation of an enhanced standard or chlorhexidine strategy compared to standard practice. Although Ramsey et al states “cost-effectiveness analysis should still be performed if the clinical study fails to demonstrate a

statistically significant difference in clinical endpoints" these failures could influence the CER as well as the ICER. Higher probability of developing an infection plays a role in the costs associated with a hygiene strategy pathway. If higher rates are observed in the chlorhexidine group compared to the standard group, one will likely see greater costs. The use of lost time in training hoped to mitigate the effects the lack of clinical significance with respect to the study. Obviously, increased risk ratios and higher costs would dominate the strategy. Within this cost-effectiveness analysis, results showed that although the chlorhexidine strategy cost more on average, fewer days were lost in training when this strategy was used compared to the standard and enhanced standard groups.

Public health impact and overall interpretation of the findings

Overall, results showed that use of a hygiene strategy that included chlorhexidine body wash was cost effective over the enhanced standard and standard study groups during the Fort Benning Study. Both total costs and effects were lower compared to the other two strategies. In fact, the costs and effects of the enhanced standard were almost twice that of the chlorhexidine group. Recommendations by local, state and federal organizations regarding the use of chlorhexidine as part of a hygiene strategy to prevent and mitigate infections and outbreaks have been mixed. Often, chlorhexidine is used only to contain an outbreak within a congregate setting among inmates and athletes. (64; 78; 172; 215) Likewise a similar strategy was employed among military trainees prior to the commencement of the prospective Fort Benning trial.(65; 146) The results derived from this study could be used to motivate public health policy with respect to the use of a personal hygiene strategy that includes chlorhexidine for the prevention of MRSA SSTI.

Caution is necessary when generalizing these results to other populations such as inmates and athletes. The prospective trial was specifically created for implementation within the military training environment. Within this environment, trainees are often motivated by their instructors and peers to comply with the strategy. Other settings may not provide such an atmosphere and compliance with the strategy could be minimal; therefore, negating the cost effectiveness of the strategy.

CONCLUSIONS

This is the first study using a decision analytic framework to generate cost-effectiveness estimates to determine the most cost effective approach to preventing SSTI overall and MRSA SSTI within a military training population. The goal of this study was to identify the hygiene strategy that averted the most costs and days lost in training. Using estimates obtained from multiple sources to include prospective and retrospective studies as well as a systematic review of the literature, CER and ICER were generated to achieve this goal. Overall, results showed that a hygiene strategy that involved both chlorhexidine and an educational component was cost-effective when compared to standard and enhanced standard groups. When evaluated by season and phase of training, the chlorhexidine approach remained cost effective compared to its counterparts during the spring and summer months during phase 1 of training. These findings are novel and could provide rationale to future approaches for the prevention of SSTI overall and MRSA SSTI in similar settings. Future prospective analysis of hygiene strategies should include cost and time components which could be used for comparisons. Further research is warranted with respect to cost-effectiveness analysis.

Table 24 Parameter estimates for primary analysis of hygiene strategies implemented at Fort Benning, GA

	Standard n=9,315	Enhanced standard n=10,864	Chlorhexidine n=10,030
Incidence SSTI overall	303 (0.03)	439 (0.04)	461 (0.05)
Incidence MRSA SSTI	86 (0.01)	135 (0.01)	95 (0.01)
Purulent	178 (59)	300 (68)	252 (55)
Non-purulent	125 (41)	139 (32)	209 (45)
Culture	158 (52)	267 (61)	225 (49)
No Culture	145 (48)	172 (39)	236 (51)
Hospitalization	12 (4.0)	10 (2.3)	11 (2.4)
Remedial training	2 (0.66)	3 (0.69)	2 (0.43)
Resolve	290 (96.0)	428 (97.7)	450 (97.6)
Complicate	12 (4.0)	10 (2.3)	11 (2.4)
Total cost of standard practice (SP)	$12.9 M	$12.9 M	$12.9M
Total cost of care for hygiene strategy (HS)	$402,629.75	$602,365.73	$575,201.88
Annualized cost averted	**$118,808.28**	**$116,906.04**	**$117,164.74**
Effects of SP (Days)	18,170	18,170	18,170
Effects of Hygiene Strategy	560	869	815
Annualized LTT (days) averted	**168**	**165**	**165**

Table 25 Base case estimates of hygiene strategies to prevent SSTI among military trainees

Strategy	Costs averted (USD)	Incremental cost	LTT (days) averted	Incremental effects	CER[1] (USD/Days)	ICER[2]
Standard	930.85		1.41		661.77	
Enhanced standard	1081.20	150.35	1.63	0.23	662.33	665.84
Chlorhexidine[2,3]	1440.88	359.80	2.17	0.54	663.83	668.37

[1]Cost effectiveness ratio (CER) and Incremental cost effectiveness ratio (ICER) [2]Includes two Incremental Cost Effectiveness Ratio (ICER) estimates in enhanced standard and chlorhexidine groups; the first number indicates the costs which include those that received the hygiene strategy but did not get infected. The second number removes those costs.

Table 26 Parameter estimates for secondary analysis (Burden of Illness vs Fort Benning Study)

	SP[1] 254,000	SPFB[2] n=64,226	Standard n=9315	Enhanced n=10,864	Chlorhexidine n=10,030
Incidence SSTI overall	20884 (8.0)	6,134 (9.6)	303 (3.0)	439 (4.0)	461 (5.0)
Incidence MRSA SSTI	2819 (1.0)	2887 (1.0)	86 (1.0)	135 (1.0)	95 (1.0)
Purulent	12958 (62)	5020 (56.5)	178 (59)	300 (68)	252 (55)
Non-purulent	7926 (38)	2121 (34.6)	125 (41)	139 (32)	209 (45)
Culture	4822 (23)	1505 (28.8)	158 (52)	267 (61)	225 (49)
No Culture	16062 (23)	4629 (71.2)	145 (48)	172 (39)	236 (51)
Hospitalization	845 (4.0)	260 (4.2)	12 (4.0)	10 (2.3)	11 (2.4)
Remedial training	354 (1.7)	66 (1.1)	2 (0.66)	3 (0.69)	2 (0.43)
Resolve	20027 (95.9)	5872 (95.7)	290 (96.0)	428 (97.7)	450 (97.6)
Complicate	857 (4.1)	262 (4.3)	12 (4.0)	10 (2.3)	11 (2.4)
Total cost of standard practice (SP)	$12.9 M/yr.	12.7 M	$402,629.75	$602,001.00	$573,836.88
Total cost of hygiene strategy (HS)	0.00	0.00		$364.73	$1365.0
Total cost of SP+HS	$12.9 M/yr.	3.2 M/yr.	$402,629.75	$602,365.73	$575,201.88
Effects of SP (Days)	19.6K/ yr.	4.5 K/yr.	560	869	815

[1]Standard practice (SP) estimates generated from IDCRP-066 Burden of Illness (BOI) Study [2]Standard practice (SP) estimates generated from IDCRP-066 Burden of Illness (BOI) Study, includes only estimates from Fort Benning (FB), Georgia OSUT

Table 27 Base case estimates secondary analysis, Fort Benning, Georgia

Strategy	Costs averted (USD)	Incremental cost	LTT (days) averted	Incremental effects	CER[1] (USD/Days)	ICER[2]
Standard	59.46	0.85	0.09	0.01	658.14	64.09
Enhanced standard	64.71	5.25	0.09	0.004	682.39	1171.51
Chlorhexidine[2,3]	58.61		0.08		760.45	

[1.] Burden of Illness (BOI) Fort Benning (FB) 2. Cost effectiveness ratio (CER) 3. Incremental cost effectiveness ratio (ICER) cost per additional increase in effectiveness

Table 28 Base-case estimates for probabilistic sensitivity analysis[1]

	Standard Practice			**Hand Hygiene Promotion**			**Chlorhexidine**			**Distribution**	**Source**
	Low	Med	High	Low	Med	High	Low	Med	High		
Incidence SSTI overall (%)	6.00	14.4	30.4	3.8	7.5	9.5	4.00	13.9	23.7	Triangular	Morrison, Elias, Goldstein
Incidence MRSA SSTI (%)	7.7	8.8	9.0	7.1	9.5	11.5	3.5	5.0	8.1	Triangular	Morrison, Elias, Goldstein
Cultured (%)	4.0	18.5	66.7	4	57	88.7	6	16	25	Triangular	Morrison, Elias, Goldstein
Hospitalization (%)	-	36	-	-	-	-	1	2	6	Triangular	Romano, Weise-Posselt
Total cost of standard practice (SP) USD	400	700	1000	400	700	1000	400	700	1000	Triangular	Sanders
Total cost of hygiene strategy (HS) USD	0.00	0.00	0.00	775	775	775	850	850	850	-	Sanders, Guinan
Total cost of SP+HS USD	400	700	1000	1175	1475	1775	1250	1550	1850	Triangular	Sanders, Guinan

[1]Estimates obtained from a systematic review of the literature

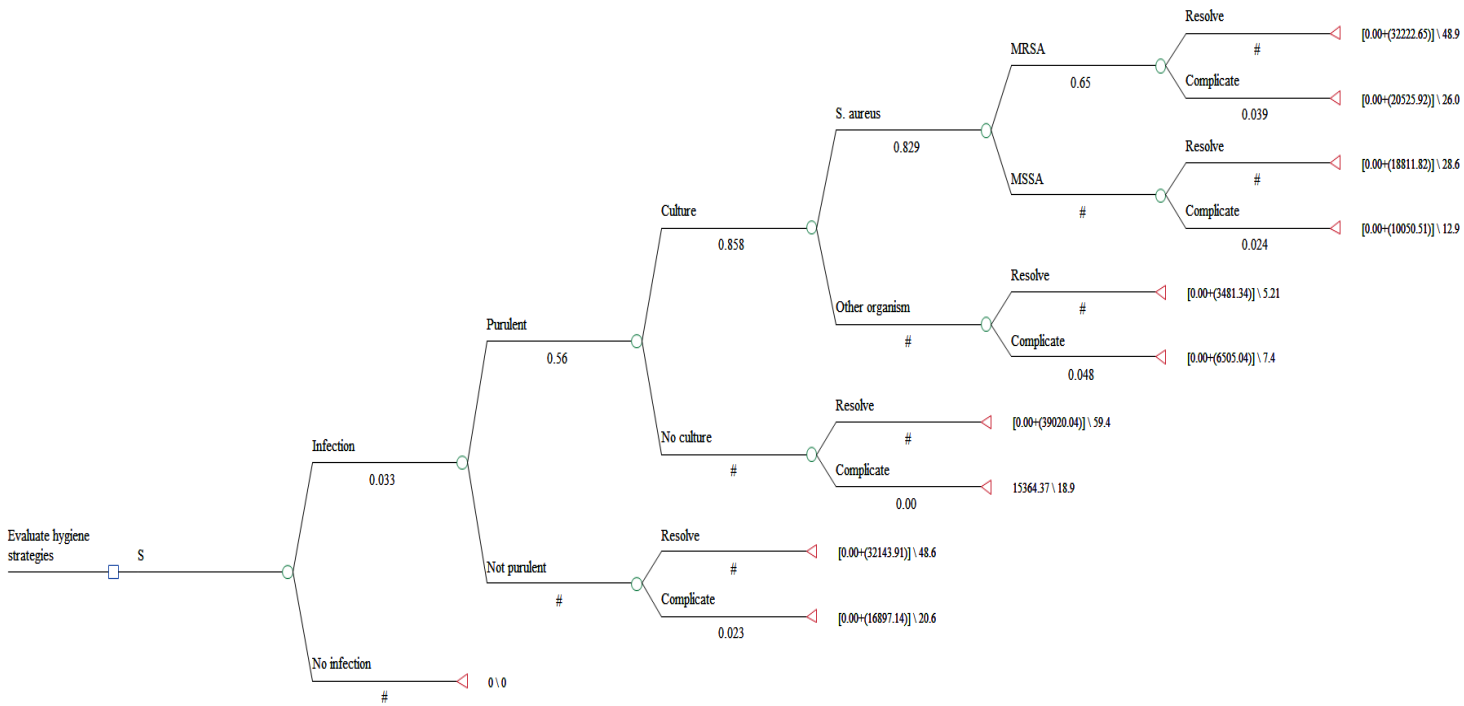


Figure 33 Decision analysis flowcharts

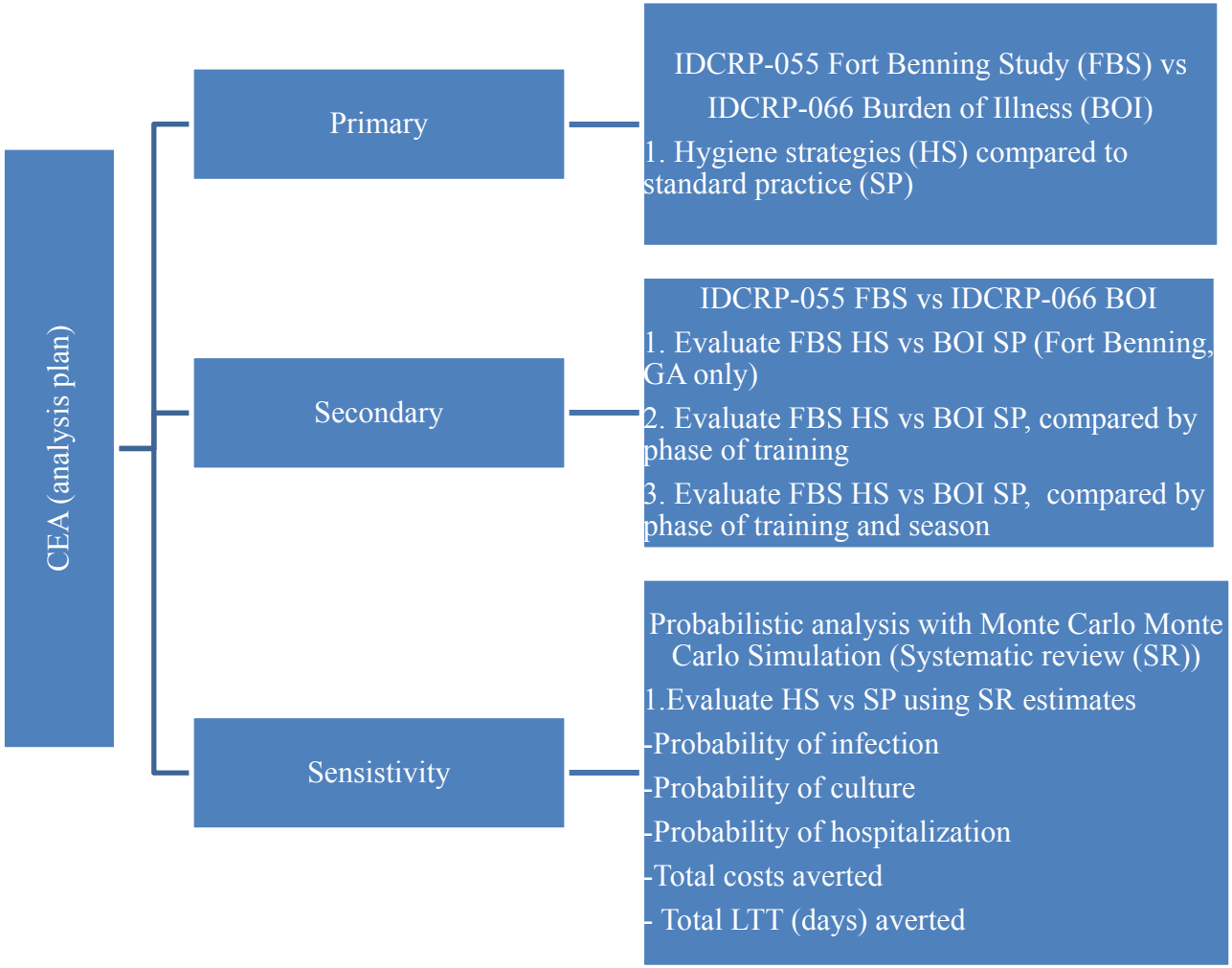


Figure 34 Cost effectiveness analysis plan

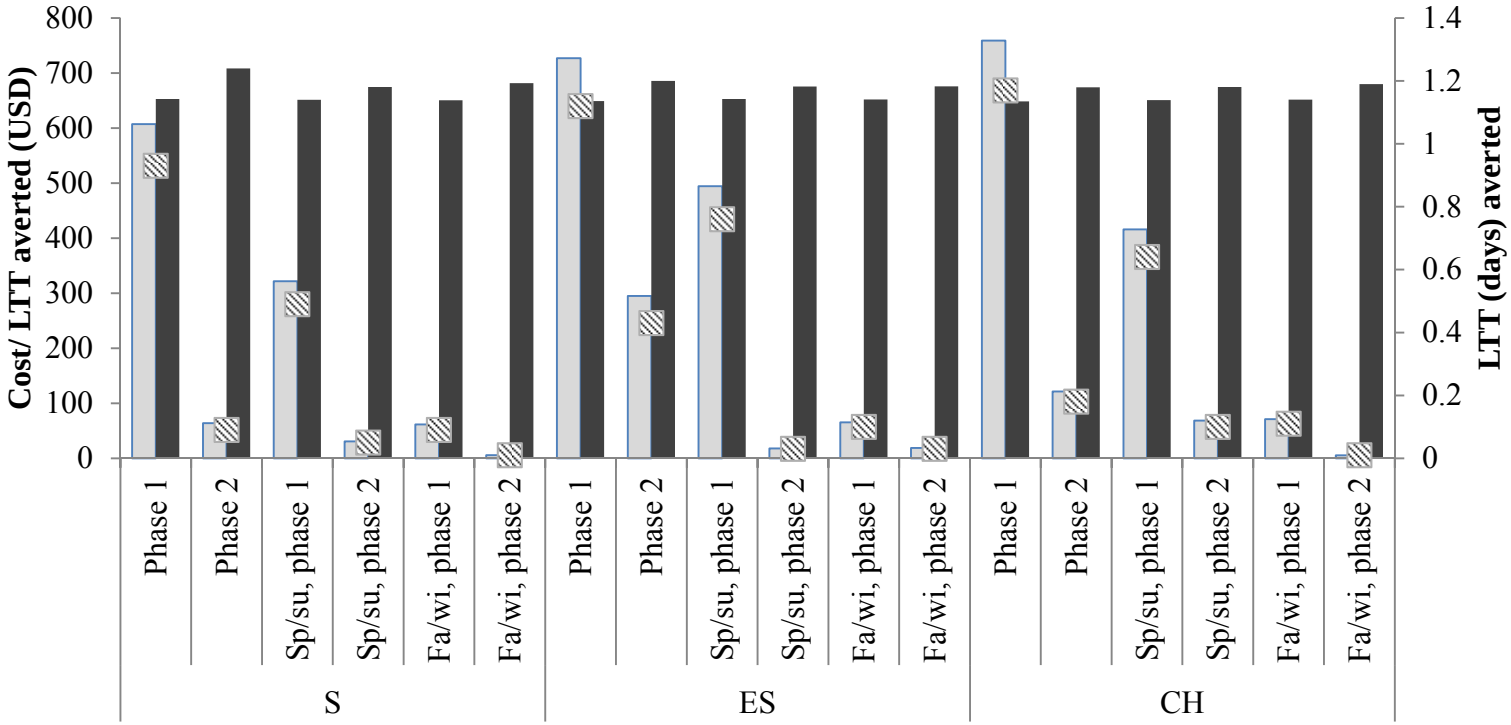


Figure 35 Secondary analyses of temporal variables [phase and season (spring/summer or fall/winter)] impact on cost (USD) and lost-time in training (LTT, days) averted per training cycle (TC=105 days); and marginal cost effectiveness ratio (CER) in each intervention group (Standard (S), Enhanced Standard (ES), and Chlorhexidine (C)). Light and dark grey bars depict cost averted and CER, respectively. White squares with diagonals represent LTT averted.

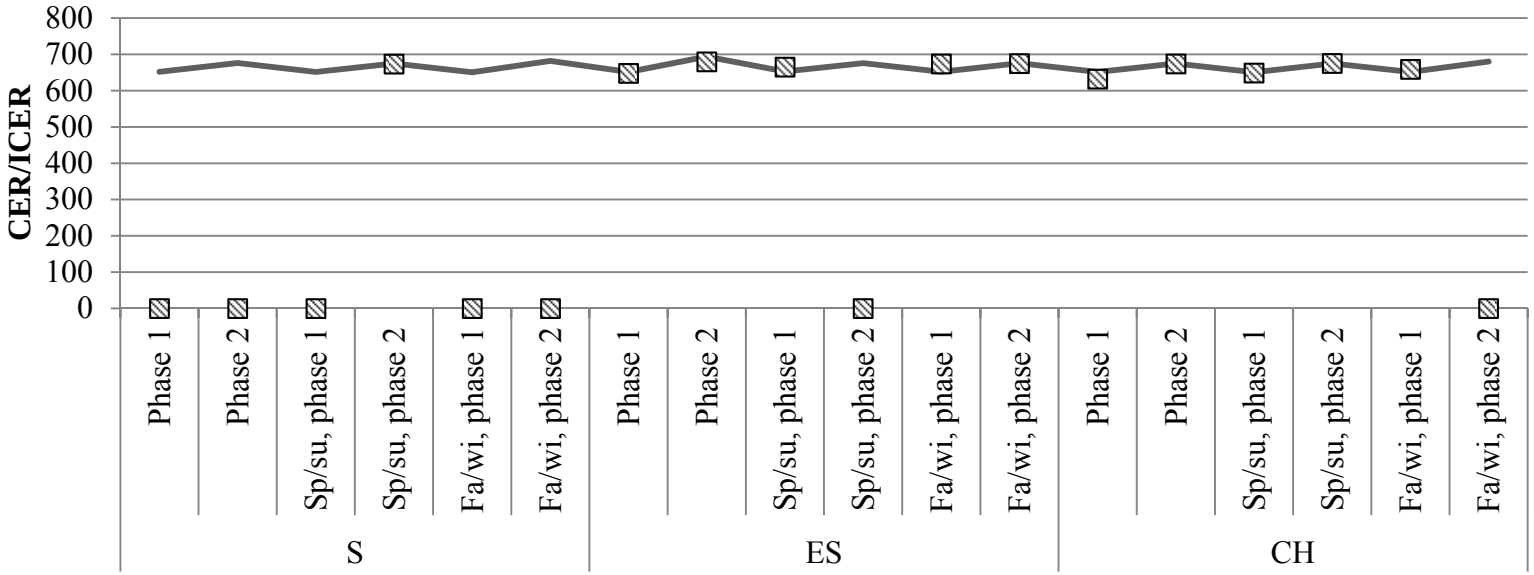


Figure 36 Secondary analyses of temporal variables [phase and season (spring/summer or fall/winter)] impact on marginal cost effectiveness ratio (CER) and incremental cost effectiveness ratio (ICER) in each intervention group (Standard (S), Enhanced Standard (ES), and Chlorhexidine (C)). Dark grey line depicts CER. White squares with diagonals represent ICER.

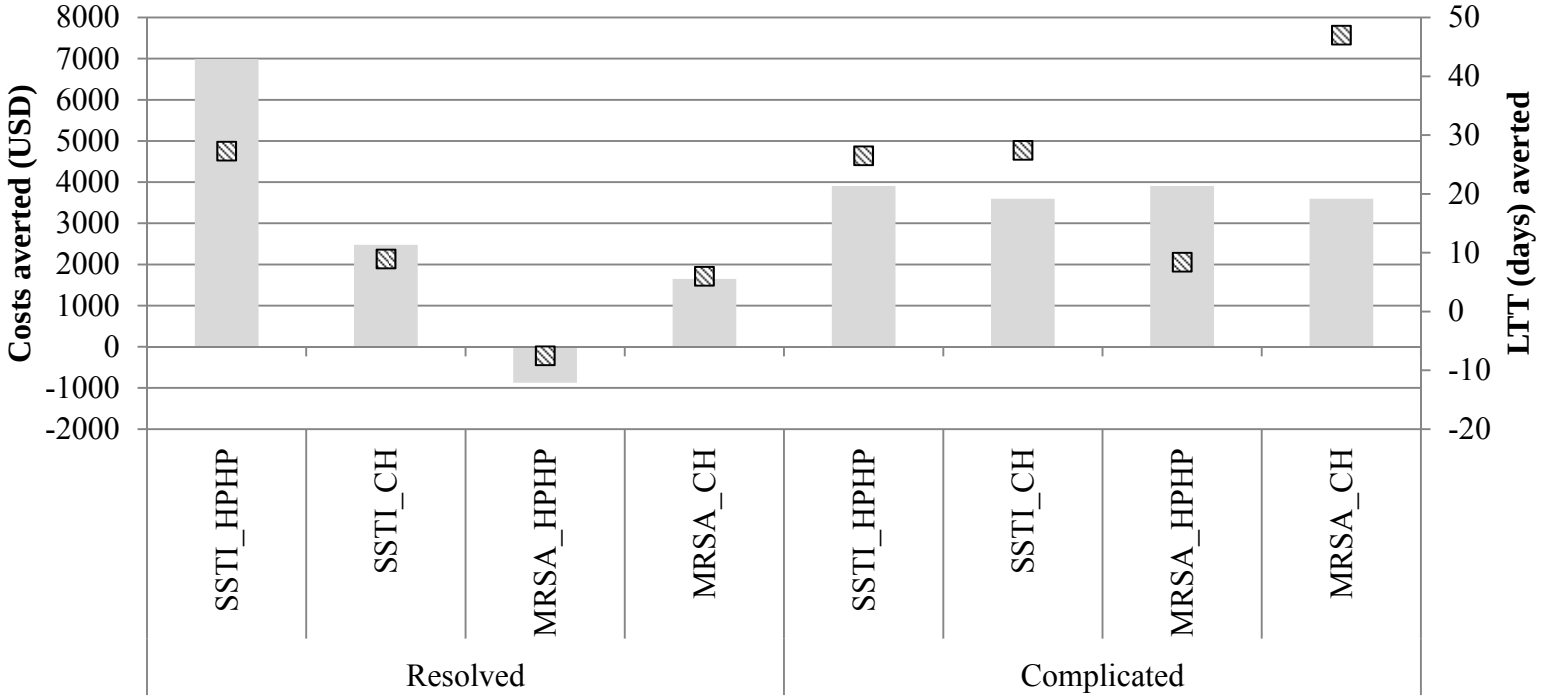


Figure 37 Monte Carlo probabilistic sensitivity analysis of cost (USD) and lost time in training (LTT, days) averted per training cycle compared by infection type (SSTI as well as resolved and complicated MRSA) and hygiene strategy (enhanced standard (ES) and chlorhexidine (c)). Light grey bars depict cost averted. Squares with diagonals represent LTT averted.

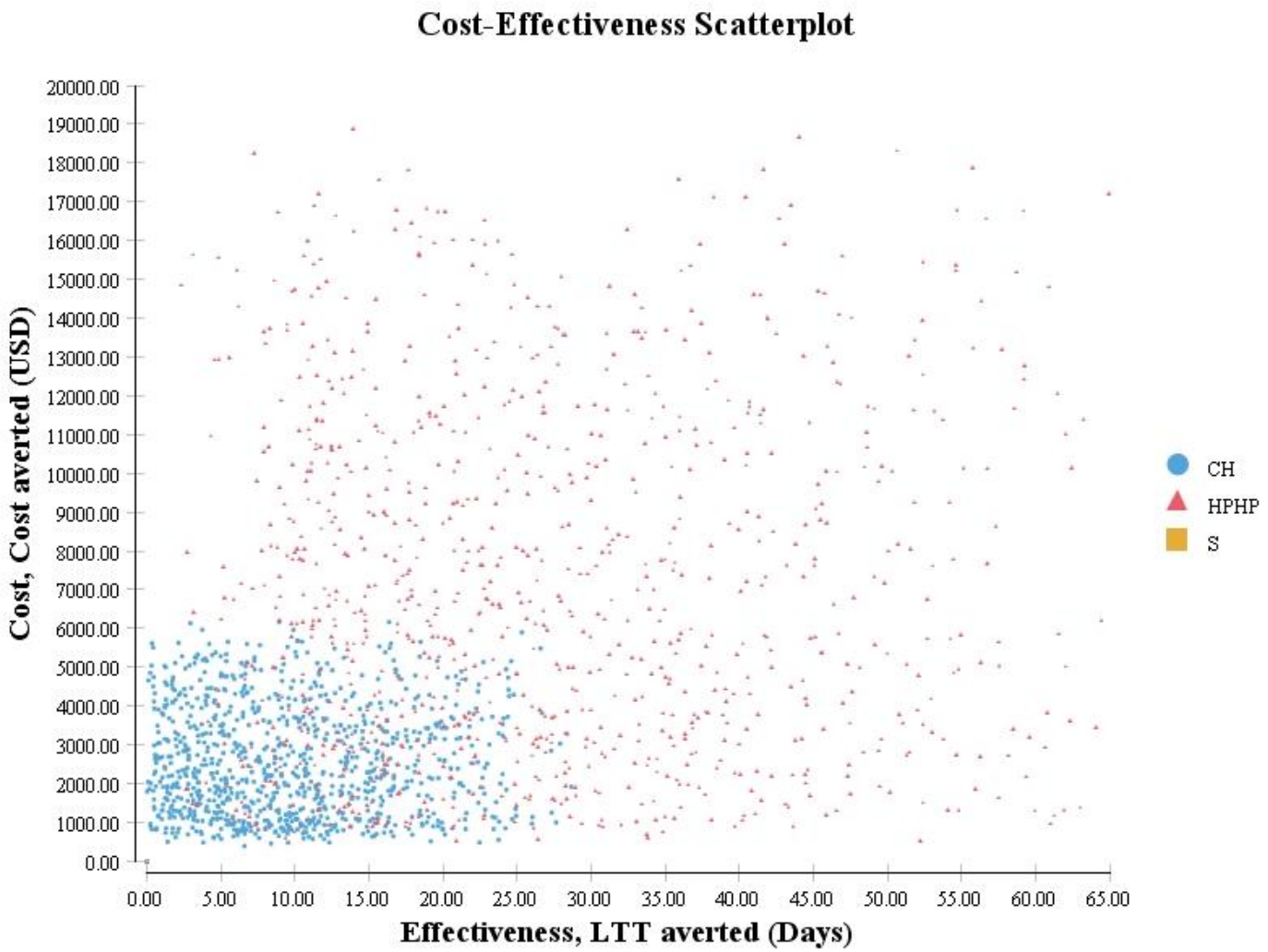


Figure 38 Scatter plot depicting costs and LTT averted among those individuals with an SSTI

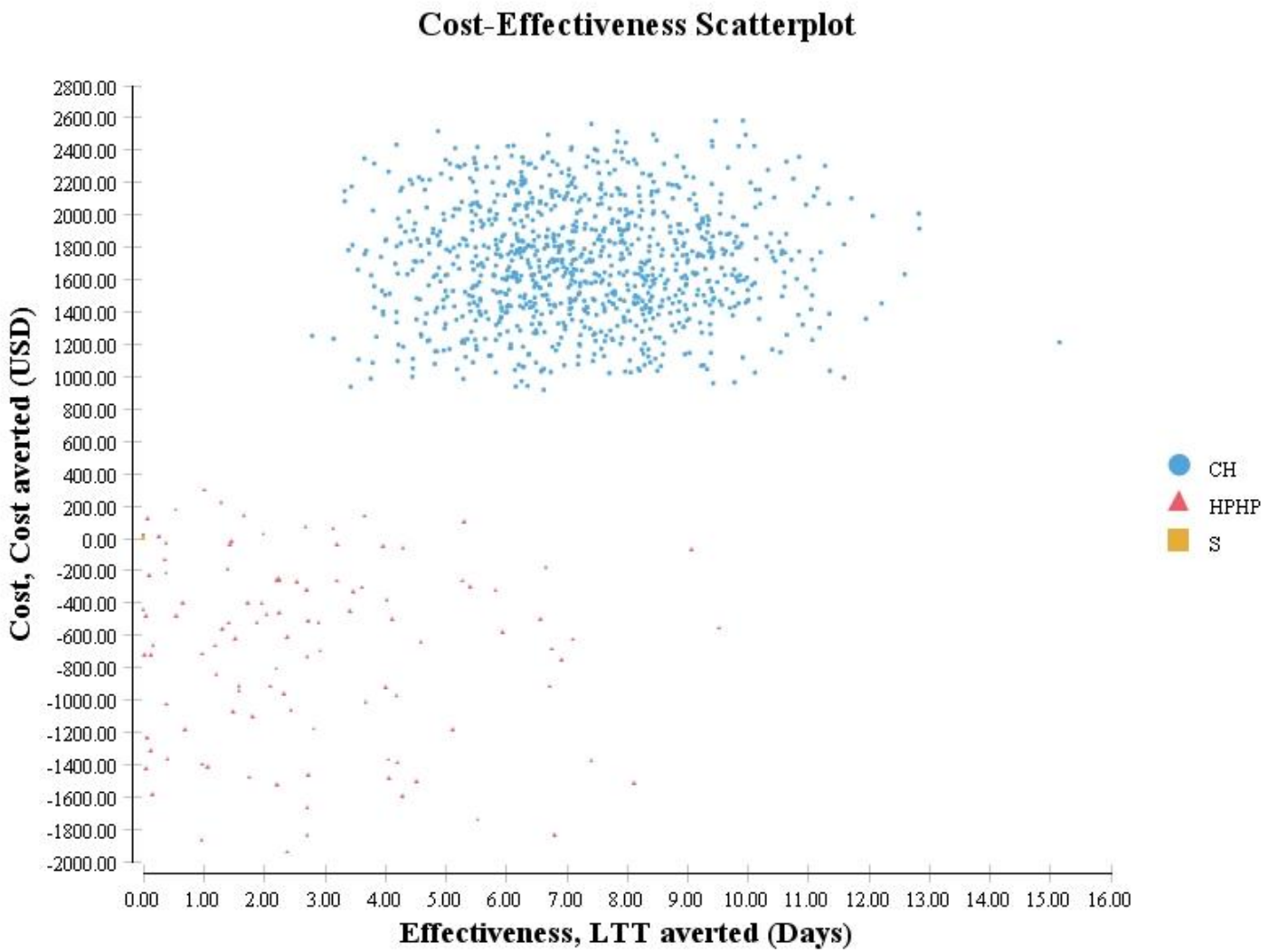


Figure 39 Scatter plot depicting cost (USD) and LTT (Days) averted among those with a MRSA SSTI

Chapter 5: Final discussion and conclusions

SUMMARY OF MAJOR FINDINGS

This novel, comprehensive study sought to explore disease, time and cost burden associated with overall, *Staphylococcus aureus* (SA) and methicillin resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infection (SSTI). Additionally, the impact of hygiene strategies on each of these measures was determined through systematic review with meta-analyses and cost-effectiveness analyses. **Figure 40** shows each piece of information necessary to fulfill this study's objectives and the major findings associated with each. The following paragraphs provide further interpretation of this study's results and their meaning in terms of public health action.

Rates of overall, *S.aureus*, and MRSA SSTI within the military population and have been comprehensively explored within other studies.(13; 114; 118; 144; 203). One study by Landrum et al (2012), studied the rates of *S.aureus* infection among TRICARE beneficiaries from 2005 through 2010.(114) They found that rates were greatest among active duty service members, ages 18-24, living in the Southern U.S. which would be expected. There were multiple differences between the Landrum study and this current study that complicate attempts for comparison of rates between civilian and military to include (1) population identification (2) data sources (3) case definition and (4) person-time estimates. These differences led to variations in results between the two studies. First, the beneficiaries were categorized into active duty service members and the non-active duty population. The active service component was not further classified by branch of service or recruits/non-recruits. An age variable was available which could have assisted in identifying the recruit population, but the definition of a trainee is also based on a trainee-specific location, time and rank. In the Landrum study, the rates of MRSA

SSTI infection were almost two times lower among the non-active duty (18-24) compared to the rates of infection in the active service component (18-24).(114)

Secondly, although the data sources used to obtained their *S.aureus* and MRSA case information was similar to this current study, rather than using a link to an ICD-9 code they used specimen source information (whether the culture had been obtained from a wound or abscess). Although this is a good approach, there could be potential cases missed because of lack of culture information. Using methods that include both clinical culture information as well as ICD-9 codes can give a general sense of cases that are being missed. Additionally, since *S.aureus* and MRSA SSTI are endemic within the active component there could be more effort in culturing and reporting of cases.

Landrum's case definition used to identify *S.aureus* and MRSA SSTI was different compared to this current study which could have led to differences in rates between the two groups as well. *S.aureus* infections were identified as all positive *S.aureus* blood, wound, and abscess cultures. MRSA SSTI were defined as an *S.aureus* positive culture with resistance toward oxacillin, cefoxitin, cefazolin, or imipenem. First, the *S.aureus* definition used a link to wound or abscess which is likely indicative of SSTI-but there are other sources of infection as well within the dataset which could have led to missed cases. Additionally, the definition of MRSA SSTI was broader in the Landrum study compared to this current study. This study only included resistance toward oxacillin plus a positive culture for *S.aureus.*

Lastly, person-time estimates to calculate rates were different between the two studies. This current study used a trainee specific time period (105 days per trainee), while the Landrum study used a "mid-year beneficiary population

identified in given calendar year" was used to calculate the person-time denominator. Based on this information, drawing comparisons between the civilian and recruit trainee population rates would be difficult.

A major component missing from the studies of overall, *S.aureus* and MRSA SSTI burden was the burden of disease within the Army training population, specifically with respect to time and military operations. A conservative lost-time in training (LTT) metric was developed to potentially operationalize burden in terms of days spent away from training because of medical care, recuperation, and training remediation. Recent military disease surveillance reports have attempted to include this metric of burden, but have not fully captured this burden among Army recruit trainees, especially with respect to remediation from training.(12; 14) The "lost work time metric" included in these reports only accounted for bed days, convalescence and time from a limited duty disposition, but did not account for training remediation.

From 2011 through 2013, military surveillance reports showed that among all eight training sites (Army, Navy, Air Force, and Marine Corps) approximately 4,500 work days were lost due to "skin disease".(14; 16; 18) It is not clear which types of skin infections specifically contributed to these lost days. Lost work time is unavailable for years prior to 2011. Results from this current study showed that the training days lost were substantial among military trainees with approximately 18,000 days being lost per year among the five Army training sites from 2006 through 2009. The number of days lost found in this current study was four times that of what was found in the military surveillance reports. It is difficult to compare the lost time in this study with what was found in the military surveillance reports. Three factors could have contributed to the

substantial difference in the number of days lost due to skin infections. First and foremost is the definition of lost work time. The surveillance report's definition did not include the recycled population. Even considering this fact, training remediation comprised 25% of the time lost in this current study. Even with the removal of the time for remediation, the annual number of days lost in training is still three times higher than what was found in the surveillance reports (13,500 days vs 4,500 days).

Another source of the potential differences in lost-time could exist in the case definition for SSTI. When the surveillance reports were reviewed, ICD-9-CM codes 680-709 were used to identify diseases of the skin and subcutaneous tissue. Similar codes were used in this study (680-686.8, and 704.8). ICD-9-CM codes are linked with hospital length of stay and disposition information (sick in quarters or released with limited duty). Considering that this current study did not include as broad of a definition of ICD-9-CM codes as did the surveillance reports, it could lead to the assumption that this current study would have underestimated the number of cases compared to the surveillance reports; thereby, undercounting the number of dispositions and the number of days lost because of the dispositions.

Lastly, differences could exist between the type of SSTI that occurred during the timeframe of this current study (2006 through 2009) and the surveillance reports from 2011 through 2013. One study noted declines in the rate of inpatient and outpatient encounters for "cellulitis" after 2006. Additionally, the rates for "other" skin infection experienced a steady increase from 2001 through 2012.(13) This finding could mean that less severe cases were occurring, leading to a decrease in the amount of time spent away

because of hospitalization and recuperation. Since this study only covers 2006 through 2009, the differences in the type of cases that occurred cannot be fully explored.

Most of the LTT burden resided in the time after initial clinical care. Work limitations and training remediation contributed to over half of the time spent away from training. On average, a trainee with a work limitation lost 1.5 days (IQR: 1.5), while a person who remediated from training lost 50 days (IQR: 4). Only 2% of the population with an SSTI was remediated, but contributed to 25% of the time spent away from training. LTT from a clinic visit comprised most of the remainder of the days lost.

These results underscore the necessity for primary prevention and adequate initial care.(13) By preventing the infection, the trainee would not have to lose on average half a day from training for a clinical visit and then the same amount of time for follow-up visits. Trainees on average had at least one follow-up visit subsequent the initial clinic visit. Additionally, prompt detection of infection can prevent further sequelae from occurring. Lastly, adequate initial care could reduce the amount of time needed to recuperate from the infection.

Both direct medical (DMC) and indirect costs (IDC) related to overall, *S.aureus*, and MRSA SSTI were calculated to derive a total cost of illness (COI) estimate for the Army training population. Results showed that total COI for SSTI overall was 51.5 million USD for the entire four year study period. Indirect costs comprised 80.5% of the total cost of illness; while DMC entailed the remainder of the costs. Work duty limitations (13.3 million USD) and training remediation (10.5 million USD) contributed substantially toward IDC. Little literature is available by which to compare this current study. A single study by Lee et al. attempted to calculate COI for community-acquired

MRSA among all Army installations from both the third-party payer (DMC) and societal prospective (DMC plus IDC). Making comparisons between these two studies is difficult for two reasons. First, the authors of Lee evaluated COI among all Army service members across all Army installations. This current study focused specifically on the Army recruit training population across five specific training sites (Fort Benning, GA; Fort Jackson, SC; Fort Knox, Kentucky; Fort Leonard Wood, MO; and Fort Sill, OK). Lee *et al.* estimated disease incidence and used estimates from the literature.(120; 144) The authors found that annual COI ranged from $14-32 million (third party payer) and $16-36 million (societal) annually. This equated to approximately $834-874 thousand annually per Army installation, of these costs $737-780 thousand were DMC. The findings from Lee et al. are the reverse of this current study's results. In the Lee study, DMC comprised over 85% of the total COI on average at an Army installation; whereby, in this current study, IDC related to MRSA SSTI encompassed the majority of the COI-approximately 78%-regardless of year or training site. Potential explanations could be based on the assumptions the authors used to obtain their IDC estimates. They only accounted for 8 hours for each day spent in the hospital and 4 hours for an outpatient visits. They did not account for time factors such as recuperating in quarters, limited duty, and training remediation. Additionally, it is unclear from the Lee study if the incidence estimates used varied by Army installation, considering the authors stated that the annual COI was for all Army installations. The annual COI for SSTI overall differed according to training installation in this current study. Greater COI was observed at larger training sites (3.1-4.9 million USD per year) and smaller training sites experienced lower COI (1.2-2.4 million per year). Secondly, their cost estimations were based on simulation

methods, whereas this study obtained actual medical and work cost estimates related to each case of SSTI from military health systems data sources. The simulation methods Lee et al. used were based on SSTI care-seeking behaviors and work productivity losses solely based on clinic visits and hospitalization. The annual COI per training site for recruit trainees in this current study is likely greater because of the methods used to estimate COI which included recuperation and training remediation costs as well as costs related to clinic and hospital visits. Annual COI for MRSA SSTI in this current study ranged between 1.34 and 2.60 million USD for larger training centers and 595 and 984 thousand USD for small training sites. Greater annual COI would be expected in the Lee study considering they evaluated the costs of MRSA SSTI for all Army service members across all Army installations.

One factor that made this current study strong was the link between clinical culture and SSTI diagnosis. Initial analyses revealed culture rates that were lower than expected. Previously reported culture rates ranged from 15% to 51% depending on the type of infection.(13; 44; 61; 65; 87; 114; 118; 137; 145; 146; 203) This current study yielded proportions between 21% for purulent infections and 19% for non-purulent infections. Considering this result, the rates of confirmed *S.aureus* and MRSA SSTI were grossly underestimated which influenced both lost time in training (LTT) and cost of illness (COI) results. After identifying this issue, measures were taken to recalculate estimates that reflected more reasonably the true burden of *S.aureus* and MRSA SSTI in terms of disease rates, time spent away from training, and costs associated with these infections. Results revealed that approximately 10,000 and 6,000 *S.aureus* and MRSA SSTI cases were potentially missed because of lack of culture. Sensitivity analyses

comparing confirmed cases to confirmed plus probable cases revealed that the missing cases influenced the results of both univariate and multivariate analyses, showing a greater *S.aureus* and MRSA SSTI burden with respect to median LTT and COI. Confirmed estimates alone showed twice to three times the LTT and COI among *S.aureus* and MRSA SSTI compared with overall SSTI. Once the probable estimates were included, the burden gap narrowed and there were only slight increases of *S.aureus* and MRSA SSTI compared to SSTI overall.

No existing multivariate analyses have been conducted to evaluate the potential independent predictors of LTT or COI within the military training population. In this study, host-specific and temporal factors as well as clinical outcomes and initial clinical care were evaluated for their association to LTT and COI. The results of multivariate analyses consistently showed that complicated SSTI, clinical culture positive for MRSA, incision and drainage procedure, training location (Fort Jackson, SC and Fort Knox, KY) were all associated with an increase in lost time in training and cost of illness ($p<0.001$). Conversely, the second phase of training, year of infection beyond 2006, training location (Fort Sill, OK), and 'African American' race were all associated with decreases in LTT and COI. These results are important as they can direct the focus of future research and public health intervention efforts for the prevention of overall, *S.aureus* and MRSA SSTI. As previously mentioned, these infections need to be prevented, but doing so is difficult. Skin is often compromised during training and the ability to implement hygiene measures to avoid these infections takes away an already limited amount of time for these trainees. Understanding when and among who these infections most commonly occur could help target prevention initiatives among trainees.

Primary prevention strategies were evaluated for their impact on rates of SSTI and MRSA SSTI. Military primary prevention recommendations include education, hand hygiene program, environmental contamination elimination, targeted treatment, as well as surveillance and screening.(154) This current study attempted to evaluate the individual and combined effects a multi-component hygiene strategy on SSTI overall and MRSA SSTI based on public health recommendations. The target populations for most of the studies found in the systematic review regarding skin infections and hygiene strategies were inmates, military service members and college athletes.(64; 78; 112; 146; 166; 172; 194; 213; 215; 216) In many of these studies, a reactive approach vice a proactive approach was taken when implementing hygiene strategies. An outbreak would occur, the institution would review guidelines and then guidelines would be implemented. No one concise method was employed, but the strategies did have common themes to include hygiene and infection education, showering with a decolonizing agent like chlorhexidine, enhanced personal hygiene (avoidance of sharing personal items and seeking care upon identification of infection).

Results from the systematic review showed that multi-component programs involving hand and personal hygiene promotion could be beneficial in preventing SSTI; although, meta-analyses revealed significant heterogeneity surrounded the pooled effect estimates. The sources of heterogeneity were explored but not identified. It was believed that the study design, population, or quality would influence the effect estimate, but analyses did not reveal evidence to support such an assumption. Potential sources of heterogeneity could be attributed to factors for which data was not collected; therefore, this result remains unexplained.

Making a recommendation to incorporate a hygiene strategy including chlorhexidine and hygiene education components into the recruit training population or similar community environment is not possible and would be erroneous. The studies used to generate the pooled effect estimate for these strategies were observational-analytic and the interventions were often implemented in response to an outbreak.(64; 114; 146; 166; 172; 215; 216) These studies were not developed in a prospective, systematic fashion; therefore, they are inherent to their own biases (information and selection) which could lead to differential effects on the study outcomes (likely showing benefit as opposed to no benefit). The results from the systematic review highlight a need for further evaluation of these strategies within a prospective setting.

This was the first study to perform cost effectiveness analysis of hygiene strategies aimed toward prevention of SSTI overall as well as *S.aureus* and MRSA SSTI within a military trainee population. There is little literature by which to compare the results.(172) Multiple cost-effectiveness analysis (CEA) models were created to calculate incremental costs and effects associated with a specific clinical pathway and the time spent away from training on that pathway. Ultimately, the ideal model would be one that averted the total costs and lost time in training associated with a pathway; meaning that if standard practice on average costs $2500 USD per infection and loses 50 days in training per infection, then the prevention strategy would have averted all costs and time associated with standard practice. Overall, the models showed that a hygiene strategy that involved the use of chlorhexidine plus education averted more costs and lost time in training days than a standard care group as well as an enhanced standard group. This is an interesting finding in that a recent prospective trial at Fort Benning Georgia among Army

recruit trainees showed no improvement in the rates of SSTI or MRSA SSTI when using chlorhexidine or enhanced standard strategies.(65) This current study evaluated cost and days averted by each strategy compared to standard practice. Probabilities are associated with each branch of the decision pathway. Lower probabilities of infection and complications equated to greater costs and days averted. Analyses revealed that within the chlorhexidine strategy group probabilities of having a purulent SSTI, a cultured SSTI, and complicated MRSA infection were lower in the chlorhexidine group compared with the enhanced standard and standard groups. This fact could have influenced the marginal and incremental cost effectiveness ratios toward the chlorhexidine strategy being more cost effective over the other two strategies. Such a result highlights the rationale that outcomes such as costs and time are important indicators of benefits and often times missing from peer-reviewed literature. Relying solely on clinical outcomes (i.e., rates) could lead to making decisions preemptively without all the pertinent information. Although the hygiene strategy that involved the use of chlorhexidine was not beneficial in terms of reducing disease outcomes, it was beneficial in averting costs and lost training time.

Secondary analyses showed that training site influenced the cost effectiveness of the hygiene strategies. The chlorhexidine group was dominated by the enhanced standard group when focusing specifically on Fort Benning. The enhanced standard group performed better, averting greater costs and time compared to chlorhexidine. The enhanced standard also averted more costs than the standard group, but the number of days averted were equivalent. An ability to evaluate cost and time averted at other training sites was not possible, as the prospective trial [IDCRP-055] occurred at Fort

Benning, GA only. One stop unit training is offered at five Army installations. Considering the chlorhexidine strategy was dominated by the enhanced standard strategy at Fort Benning (based on secondary analyses), further evaluation is warranted to determine which hygiene strategy is most cost effective at the specific training sites. Identifying the factors that make a strategy cost effective at certain training sites is important in the development and implementation of hygiene strategies in the training population.

Additionally, phase and season of training changed the cost effectiveness results. The chlorhexidine strategy was most cost effective during phase 1 alone, spring and summer season of phase 2, and during the fall and winter of phase 1. The enhanced standard strategy, on the other hand, was more cost effective during phase 2 alone as well as spring and summer of phase 1 and fall and winter of phase 2 compared to the other two strategies. Results from the prospective trial at Fort Benning, GA showed higher rates of MRSA SSTI during phase 1 of training in the chlorhexidine group compared to the other two groups, which contradicts the finding of more cost and time loss averted found in the cost effectiveness analysis.(65) As mentioned previously, along the infection pathway there are probabilities, costs, and time factors that are associated with each branch of the decision tree which motivate the results. Although the chlorhexidine strategy was not clinically beneficial in reducing rates of infection, it did lead to averting greater costs and lost time in training during phase 1 of training compared to the other strategies. One result that was consistent between the two studies is the fact that MRSA SSTI rates were lower during phase 2 in the summer within the chlorhexidine group compared to the enhanced standard group. The chlorhexidine strategy was more cost effective than the

two other strategies during this same time period. Ultimately, season and phase of training influenced the effectiveness of the hygiene strategy both in terms of rate reduction as well as costs and lost time in training averted. The question remains-why? Why do these temporal factors have such an impact on these outcomes? Seasonal variations in overall and MRSA SSTI rates have been observed previously and are not unexpected.(118; 200) These variations likely contributed to the cost and lost time in training averted along the infection pathway as the probabilities of infection, culture rates, and complication all contribute to the cost effectiveness ratio. One point made from the prospective trial [IDCRP-055] was trainees from the enhanced standard group and chlorhexidine group might have sought care earlier in training compared to those in the standard group.(65) If this is the case, this could explain the difference in the cost effectiveness with respect to phase of training. Trainees seeking care earlier could have avoided further disease sequelae which in turn could have averted costs and time associated with convalescence and training remediation.

STRENGTHS

This study has multiple strengths. First, the size of the population to explore the burden of disease in terms of rates, lost time in training, and cost of illness is extensive. The dataset covered a four year period including the trainee population from all five Army training facilities. Additionally, the military health systems (MHS) datasets were robust. These datasets provided individual level, granular disease and cost data for each case of SSTI among the recruit trainees. The MHS data also provided a link between the ICD-9-CM codes for SSTI and clinical culture information. Previous surveillance reports attempted to evaluate the burden of SSTI within the military population, but have been

limited in their evaluation of *S.aureus* and MRSA specific SSTI because of lack of microbiology data. This study went beyond investigating burden solely based on clinical outcomes and operationalized the burden in terms of time and costs outcomes. With respect to costs, most cost of illness studies only capture direct medical costs. With the inclusion of a time component, this study was able to derive indirect cost estimates. Without such measures, the COI would have been grossly underestimated. The multivariate analysis evaluating predictors of lost time in training and cost of illness related to overall, *S.aureus* and MRSA SSTI provided insight as to target times for hygiene strategy implementation. Furthermore, the MVA highlighted potential factors that could be indicators for disease severity. The results from these analyses could be used to inform public health research and practice. Lastly, results from the cost effectiveness analysis showed that although there is benefit in a hygiene strategy that includes a chlorhexidine component, temporal variations influence its cost effectiveness. Additionally, sensitivity analysis showed that the type of infection (SSTI overall or MRSA SSTI) is important in determining the type of strategy to use. These initial results indicate that further research is warranted in the hygiene strategies are cost effective in terms of cost and time averted, but no effects were observed with respect to rate reduction.

LIMITATIONS

Parts of this research used retrospective data, so this could lead to systematic error such as selection and information bias. Data were not collected systematically, but data used were from military health systems (MHS) data sources which are granular and robust. Individual level person-time information collected from MHS was used to

calculate rates of overall, *S.aureus* and MRSA SSTI. Person-time estimates from January through March 2006 were much lower compared to the same months during the remainder of the study years (2007-2009). This variation in person-time could have overestimated the rates during this time period; therefore, an average person-time was calculated for these months in order to reduce the potential for overestimation.

ICD-9-CM codes were used to identify SSTI cases in the IDCRP-066 burden study as opposed to use of clinical assessment. Miscoding could have occurred and cases could have been missed. A strategy was developed to follow the case within a 30 day window, but error cannot be excluded. Sensitivity analyses were not performed to determine if diagnostic coding differed by training site as well. Additionally, information regarding purulent and non-purulent infection variable was based on ICD-9-CM codes. "Cellulitis and abscess" are coded together; they are not pathogen specific. Distinguishing between the two was based on linkage with an incision and drainage procedure code (which is indicative of an abscess) as well as clinical microbiology information. If microbiology information was associated with the cellulitis and abscess, the reasonable assumption was the infection was likely related to an abscess and in turn, purulent. These assumptions could have led to an over or underestimation of purulent and non-purulent cases.

The methods used to generate lost time in training (LTT) and cost of illness (COI) metrics were novel and there is a limited literature base by which to compare the findings. Further, LTT and COI included the recycled population (i.e. those trainees who remediated training). Inclusion of this unique subgroup could have led to an underestimation or overestimation of both the number of days lost in training as well as

indirect costs associated with SSTI. Assumptions used to create the recycled population variable were derived from authoritative military doctrine as well as field expertise (TRADOC Regulation 350-6; AR 612–201 24 February 2011; TRADOC regulation 350-10 Institution Leader Training and Education, Chapter 2 part 12; TRADOC regulation 350-10 Army School Policy, Chapter 3 part 31). Factors included in the "recycled" lost time variable were length of stay (>=4 days), convalescence (30 days), and remediation (14 days). Sensitivity analyses were performed to determine the number of days expected for a trainee to remediate training (0-21 days). These analyses showed that the differences in mean LTT annually did not vary too much across the three categories (0, 14 and 21 days). Total annual LTT ranged from 15-17 thousand days lost per year for 0 days of remediation and 17-19 days lost per year for 21 days of remediation. Similar results were observed with sensitivity analysis of COI. Average COI annually ranged from 1700-1900 USD per case annually and 1800-2200 USD per case annually for 0 and 21 days remediation, respectively. At least a portion of training would necessitate remediation; therefore, a conservative estimate of 14 days was chosen that possibly reduced error associated with under or overestimation.

One limitation of the systematic review was only one reviewer performed a literature search, extracted the data, and entered the data into the database. Selection and information bias could have occurred at each of these steps. The one reviewer used her judgment as to the literature that was suitable for inclusion into the analysis and individual perception and biases could have led to error. Search strategies and terms were based on previous, similar systematic reviews.(5; 63; 90; 102) Additionally, since only one reviewer entered data into the system, the reviewer could have misclassified,

miscalculated or mistyped information during data entry. Validation rules were instituted in order to limit entry error., A previously created and validated data tool was also used to collect data.(135) During the quality assessment, two reviewers assessed the quality of a 10% sample of the literature obtained during the literature search. The reviewers' scores were compared and agreement was obtained on most of the questions. With respect to the questions in which agreement was not obtained, the questions were reviewed and discussed. Another limitation of the systematic review was the type of studies that were included. Because of the nature of the interventions evaluated, multiple case-control and prospective cohort studies were included within the analysis. The observational nature of these studies usually leads to an overestimation of the beneficial effect of the intervention under study. As previously mentioned, significant heterogeneity was found which limits the use of the pooled estimate.

Additionally, during the prospective trial, cost information was not collected. Average cost of care for overall SSTI was used to generate the costs associated with each SSTI that developed within the prospective study. Since the actual costs for each case was not available for the prospective study, this fact could have influenced the results of the cost-effectiveness analysis. Costs were calculated for each branch of the decision tree specific to the hygiene strategy. Overestimation of costs could have shown that a certain strategy was not cost effective; conversely, underestimation of costs could have resulted in an erroneous finding that the hygiene strategy was cost effective. Conservative cost estimates were used to reduce this potential bias.

Lastly, each component of this evaluation was used to perform cost effectiveness analysis. The under or overestimation of the rates, lost time in training, cost of illness, or

risk ratios could have a differential effect on the cost effectiveness calculations. As was previously mentioned, every effort was made to approach assumptions and calculations conservatively; therefore, likely underestimating outcomes as opposed to overstating the burden and effects of the hygiene strategies.

PUBLIC AND MILITARY HEALTH RECOMMENDATIONS

The goal of primary prevention is to stop the infection before the disease occurs. Much of the public health research and prevention efforts aimed toward skin and soft tissue infections with *Staphylococcus aureus* involvement have provided results with varied effects. Prospective evaluations of hygiene strategies resulted in no benefit (65; 213); while retrospective analyses claimed reductions in disease (146). Ultimately, a prevention strategy needs to be effective and not cost prohibitive. Additionally, the strategy needs to be sustainable and one in which people within the community will continue in daily practice. A need may exist to explore prevention efforts beyond hygiene strategies and environmental decontamination. One study reviewed prevention and control efforts associated with community-acquired MRSA. Authors briefly highlighted the need for hand washing and surface decontamination, but also presented a case for immunization and vaccines. (184) A vaccine for *Staphylococcus aureus* is not available, but research is currently underway in this area. Much discussion has occurred regarding the need for a vaccine, but the time horizon as to when a vaccine would be available is unclear. Results from this current study's cost-effectiveness analysis showed that hygiene strategies are costly and their effects vary. Future cost-effectiveness analyses should incorporate a vaccine strategy within the model to determine if vaccinating high-risk populations, such as military trainees, would be cost-effective or prohibitive. This information could direct allocation and distribution of future medical and work resources. Studies of this nature have been conducted and can be useful to policy makers.

Total disease, time, and cost burden of overall, *S.aureus*, and MRSA SSTI is substantial within the military trainee population and should be prioritized for risk mitigation strategies. Within this study, the annual trend observed seems to be pointing toward a decline in time and cost burden; although, without an evaluation of the data beyond this current study's timeframe from 2006-2009, it is difficult to speculate as to which direction the trend will continue. Considering this fact, it is important to continue to make strides in future research endeavors and formulate public health intervention and prevention efforts aimed toward this acute infection. As aforementioned, guidelines for prevention of community-acquired infections such as MRSA SSTI have been documented by local, state, and federal organizations. These guidelines point to hand washing, personal hygiene measures and environmental sanitation as practical means by which to prevent infections from entering the human but also as a way to limit transmission. In theory, these means are practical, in the training setting, such measures are often impractical. Trainees' stringent schedules often do not allow for the time required to address personal hygiene or early detection of infections. Additionally, it is a common practice to share products such as towels, razors, etc., which can lead to further spread of disease. One report recommended a focus on the host-agent-environment triangle when evaluating practices to prevent SSTI with MRSA involvement.(13) Within this research effort, the host and the agent were considered, but prevention strategies for decontaminating the training environment were not fully explored. Fomites are considered to be a conduit for spreading infection in high risk, congregate community settings. (140) Daily cleaning routines are supposed to occur during training. The addition of a cleaning policy aimed toward eliminating the *Staphylococcus aureus*

organism on surfaces should be evaluated further as limited research is available in this area. Such a practice likely would not diminish training time if this is an already ongoing practice within the daily routine.

Additionally, with respect to time restrictions within the military training environment, the results from this study can assist with targeting the implementation of strategies during specific training periods. Results of the epidemiologic and economic burden study showed that phase 1 of training influenced rates, days, and costs associated with overall, *S.aureus*, and MRSA SSTI. During cost effectiveness analyses it was revealed that use of certain strategies, such as one with chlorhexidine and education, would be preferred over other strategies during training phase 2 during the summer months. Instead of employing these strategies on a grand scale during all training cycles, they should be implemented only during high-risk times. Using a strategic approach like this could reduce costs associated with the prevention program and potentially could be beneficial in preventing infection and lost-time in training.

Future studies with respect to prevention of SSTI with *Staphylococcus aureus* involvement should include metrics that are operational. Effects of disease in terms of days lost and costs involved with diminished work productivity are useful to individuals at multiple levels within the training command. Associating a disease with time and costs components could be easier to understand as opposed to solely rates and relative risks of disease. When developing data collection tools for future, prospective studies, these metrics should be included to adequately capture the true time and costs of disease, and hopefully avoid the potential for error related to under or over-estimating effects.

A brief review of surveillance reports from 2010 through 2014 was performed to evaluate where in the scope of disease burden SSTI overall places with respect to illness and injury burden among trainees. (12; 14; 16; 18; 40)These reports review medical encounters and hospital bed days for ICD-9-CM specific codes, additionally from 2011 through 2013; an attempt was made to calculate lost work time among trainees. (14; 15; 18) Medical encounters and lost work time were highest for respiratory infections and "injury and poisoning" among trainees at training sites among all four branches of service. (**Figure 41**) Skin disease continuously placed 4th with respect to medical encounters and bed days and placed 5th for lost work time. In terms of public health priorities in the training environment, research efforts toward primary prevention of SSTI may not at first glance seem to be at the top. Considering that recommendations to prevent or control SSTI are similar for preventing other infections (i.e., respiratory) finding alternative prevention or risk mitigation strategies might be worth pursuing. Medical encounters for respiratory infections experienced a steep decline from 2009 through 2013, but encounters remained stable for skin infections. Understanding the approaches taken to reduce the burden of respiratory infection could be helpful in reducing the burden of skin infections.

A commentary in April 2012 edition of the Medical Surveillance Monthly report discussed military importance and its determinants.(20) Authors categorized the determinants into costs, effects, compassion, and concerns for the public. These guidelines could prove useful when prioritizing decisions at multiple levels within the military. In terms of military importance this research covered each of the above determinants. First, with the burden of illness study, covered the effects of the disease on

the recruit training population in terms of lost time in training as well as rates. The lost time in training metric is operational in that it shows the effect of the disease in terms of the number of days a trainee loses when the individual has a SSTI with *S.aureus* or MRSA involvement. The number of days lost was quite significant with respect to work duty limitations and training remediation. This information is valuable to trainees and their commanders as it shows the importance of stopping the infection before it occurs. Secondly, this study calculated both direct medical and indirect costs to derive an overall cost of illness measure. In doing so, results showed that indirect costs contribute significantly to the burden of this disease within the military training population. Greater understanding of the position of these costs with respect to other communicable illnesses is important so the complete scope of the problem is covered. Additionally, this study attempted to identify measures that could potentially prevent these infections from occurring within this population. Although results are mixed it is the first step in identifying strategies to prevent infections in the future. Last, this is an issue of concern within the general public as well as among military members. These infections have gone beyond the hospital setting and have planted themselves squarely into the community population. Although the highest risks for these infections are in congregate community settings among healthy individuals, these infections have been noted outside of this population. (114; 137; 207)

Although the results of this study did not provide a clear intervention strategy to incorporate within the recruit military training environment for the prevention of SSTI, it did establish a methodology going forward to evaluate burden of illness within this population. Burden not only with respect to overall, *S.aureus*, and MRSA SSTI, but

burden attributed to other diseases as well. The approaches used within this study, such as the calculation of the operational outcomes lost time in training and cost of illness, should be applied within future military medical surveillance as well as prospective studies. These two metrics included information with respect to the remediate population that had not been evaluated previously. These estimates provide tangible figures important for policy development and the decision making process as they are tangible and provide a more complete assessment of the actual burden of disease within this population. The public health surveillance community, specifically military medical surveillance, should move forward to incorporate such methods into their surveillance activities.

CONCLUSIONS

This novel, comprehensive evaluation set out to identify a cost-effective approach to prevent overall, *S.aureus*, and MRSA SSTI from occurring within the Army recruit training population. Major research findings revealed that the burden of these infections is costly in terms of days and dollars expended. Finding a prevention strategy is important to both trainees and their command. These infections compromise the trainees' ability to complete training and in turn the military's force readiness. These research findings can be used at multiple levels within the field of public health as well as military health and training system. Future research efforts should include time and cost metrics to provide a more adequate picture of burden not only within the military setting but similar environments. Within the military setting, these analyses should be extended beyond the Army training population. Additionally, cost-effectiveness analyses should not end here; rather, evaluations should incorporate a hypothetical model that projects the cost-effectiveness of *Staphylococcus aureus* vaccines compared to standard of care and

recommended hygiene practices. All these efforts combined can assist in prioritizing research efforts and public health interventions as well as the distribution of medical services and care.

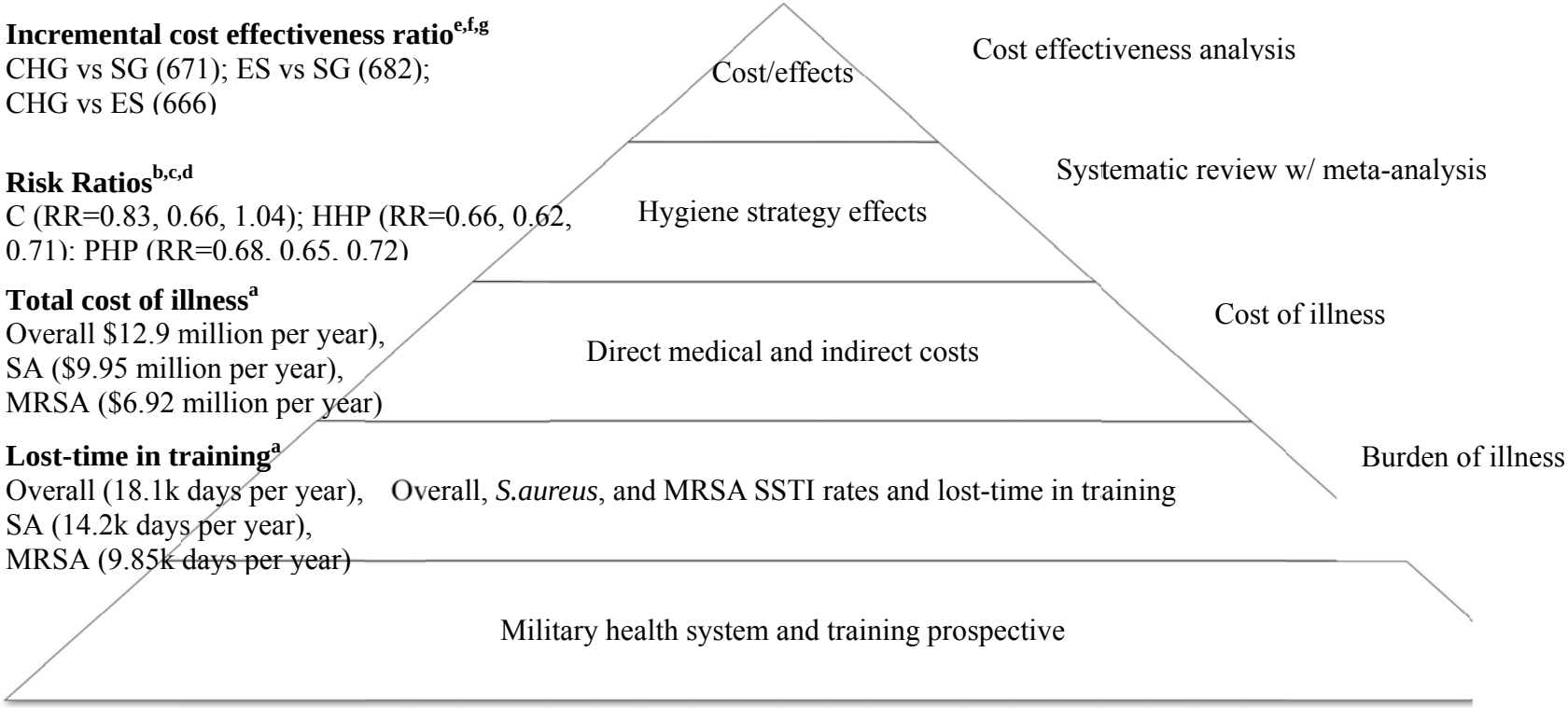


Figure 40 Overall study effects. aS.aureus (SA); bChlorhexidine (C); cHand hygiene promotion(HHP); dPersonal hygiene promotion(PHP); eCHG (Chlorhexidine group); fEnhanced Standard (ES); gStandard Group (SG)

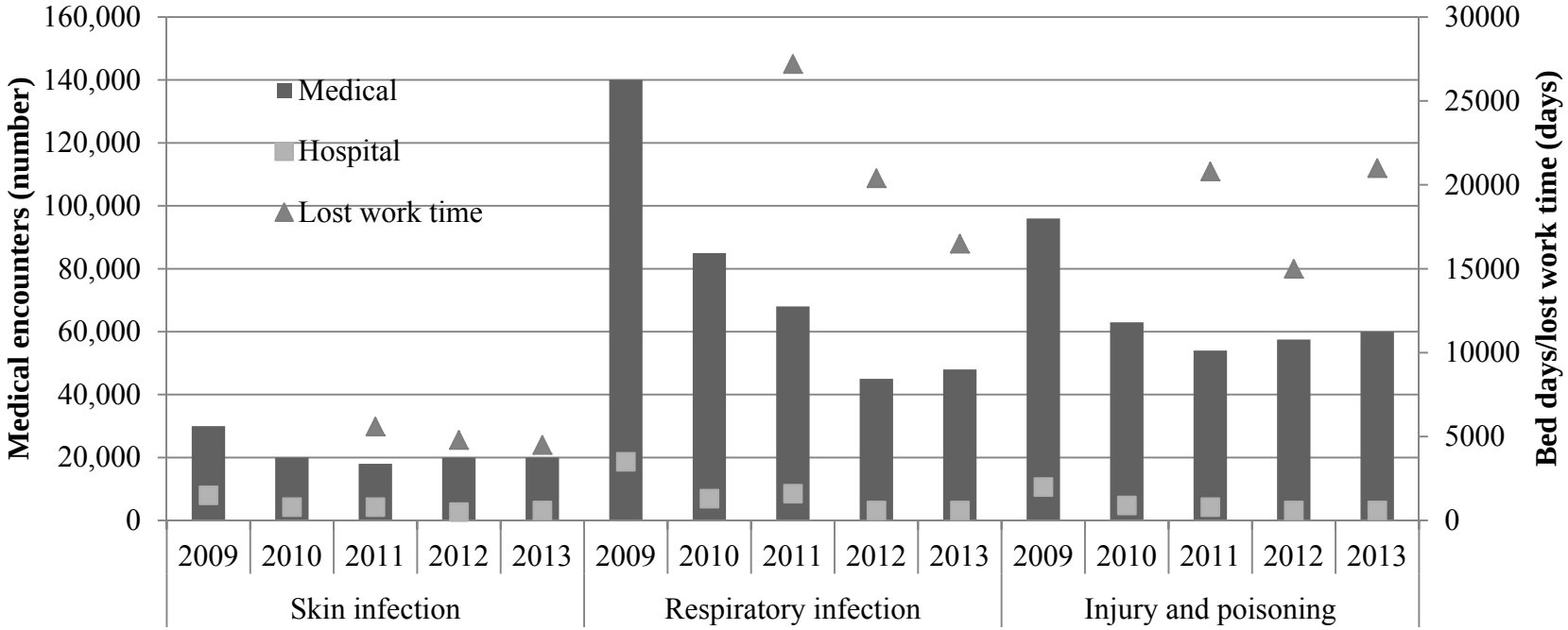


Figure 41 Comparison of disease burden among trainees from 2009 through 2013.(12; 14; 16; 18; 40)

Appendix A Literature review of cost of illness studies

Author, study design, population, & year (s)	Infection type (s) evaluated	Datasets used, pertinent measures, outcomes,
Marton, et al. • Retrospective cost analysis • In- and outpatient records • N=1997 • 2002-2005	Evaluated 'skin and skin structure infections' due to MRSA. Used ICD-9 codes, including: • Cellulitis & abscess of finger and toe • Other cellulitis& abscess • Acute lymphadenitis • Decubitus ulcer • Ulcer of lower limbs • Chronic Ulcer specified sites • Chronic Ulcer unspecified site • *Staphylococcus aureus*	- Managed care claims database - Healthcare utilization (e.g. percent with 1 or more hospitalizations, mean number of re-hospitalizations, percent using lab tests and procedures, mean number of lab tests and procedures) - Mean healthcare costs: total (SSSI- specific) • Inpatient: $3,533 ($1,583) • Outpatient: $2,241 ($1,167) • Pharmacy: $1,758 ($1,132) • **Total: $8,865 ($4,551)**
Dehkharghani, et al. • Assessed economic burden of skin disease in the U.S. • In- and outpatient records • 1997	Evaluated disease using ICD-9-CM codes, including: • Primary diseases of the skin, 680-709	- 1996 Medical Expenditures Panel Survey (MEPS); 1997 National Hospital Discharge Summary; IMS Health; 1997 AC-Nielsen;1998 National Ambulatory Medical Care Survey; 1996 National Health Interview Survey -No. of ambulatory visits, inpatient discharges; bed days - Costs, including: • Ambulatory visit: $19.8 billion (b) • Inpatient: $ 7.2 b • Prescription drug: $3.0 b
Filice, et al. • Retrospective study, Department of Veterans Affairs	*S. aureus* illness classification based National Nosocomial Infections Surveillance system definitions.	- VA electronic clinical patient record system and Decision Support System -Inpatient & outpatient utilization

• N=725 • January 2004 through June 2006	Cost comparison between patients infected with MRSA and MSSA	-Median healthcare costs, including: • Overall inpatient costs $26,274 vs. $6,748 • Overall outpatient costs
Menzin, et al. • Retrospective analysis • Hospitalized patients • Conducted between January 2005 and June 2006	Evaluated 'skin and skin structure infections' due to MRSA. Used ICD-9 codes, including: • Cellulitis & abscess of finger and toe • Other cellulitis& abscess • Acute lymphadenitis • Decubitus ulcer • Ulcer of lower limbs • Chronic Ulcer specified sites • Chronic Ulcer unspecified site • *Staphylococcus aureus*	- Premier Perspective database -Duration of antibiotic therapy, antibiotic switching, hospital length of stay, mortality, and mean costs. -Mean costs • Room and board: $3,417 • Antibiotics: $611 • Laboratory: $504 • **Total costs $6,830**
Kopp, et. Al • Retrospective, case-control analysis • Patients at an academic medical center • Conducted between January	Diagnosis of *S. aureus* infection who received appropriate antimicrobial therapy for at least 24 hours were eligible. Cost comparison between patients infected with **MRSA and MSSA**	- Matched chart review -Clinical outcomes • Hospital length of stay (LOS), days antibiotic LOS, days; ICU LOS, days; duration of mechanical ventilation, days -Economic outcomes • Hospital cost: $16,575 vs. $12,862

Appendix B Recommendations issued for prevention and control of MRSA-associated infections

	CHXD[1] Wash	Hand Hygiene[2]	Personal Hygiene[3]	Education[4]	Environmental Sanitation[5]	Periodic Lab Surveillance/skin inspection[6]
SHEA		x		x	x	x-lab culture
CDC		x	x		x	
NMCPHC		x	x	x	x	x-lab culture and skin inspection
APHC		x	x		x	
USMC RTC	x	x	x	x		x-lab culture and skin inspection
FBOP		x	x	x	x	x-lab culture and skin inspection
NCCA		x	x	x	x	x-lab culture and skin inspection

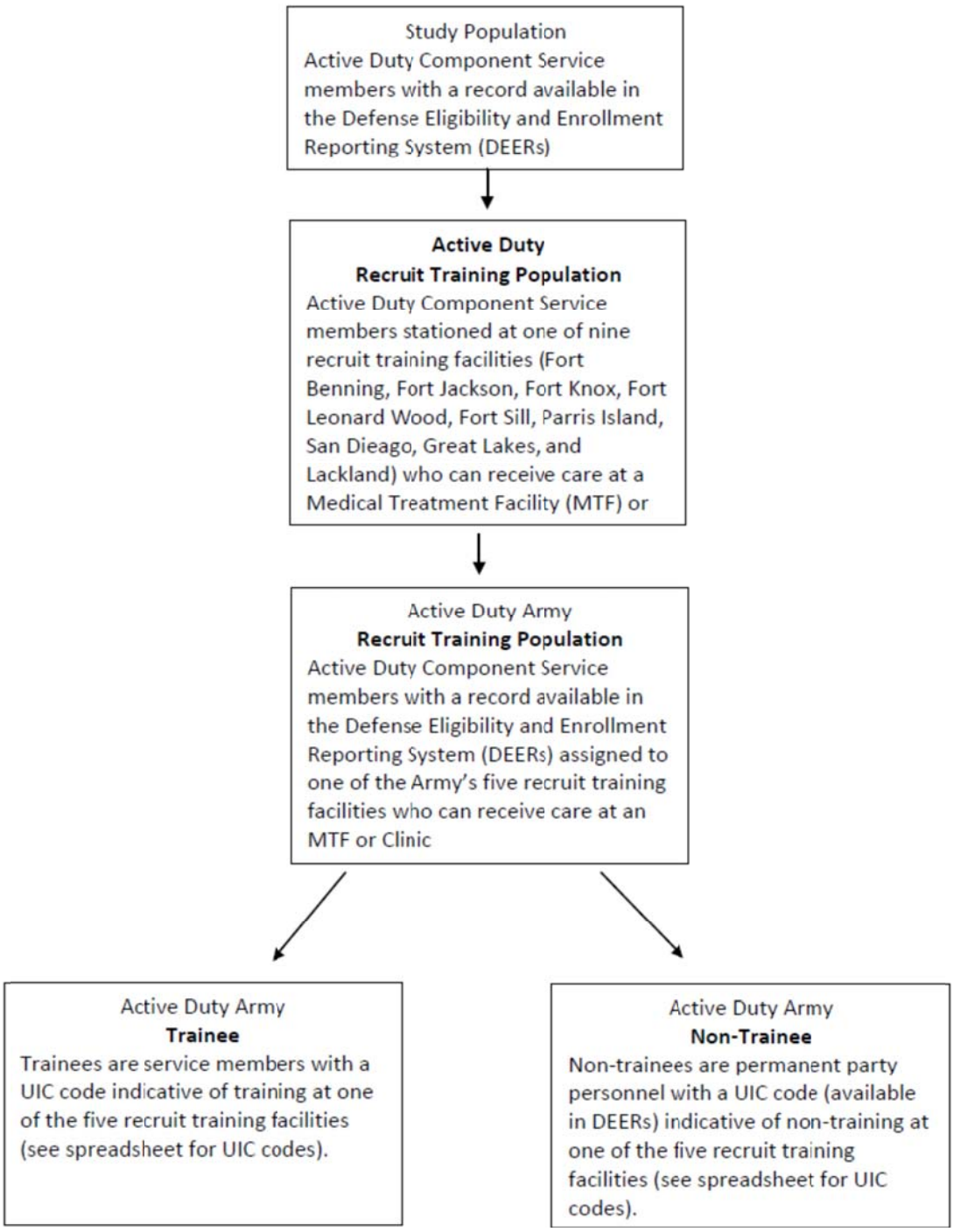
[1] CHXD wash: Shower or wipe with a chlorhexidine gluconate solution such as Hibiclens [2] Hand hygiene: Use of soap and water, hand sanitizer, or soap with an antimicrobial agent [3] Personal hygiene: Adequate shower, access to soap and water, refrain from sharing personal items, wound contact avoidance, wound cleanliness, contact limitations [4] Education: MRSA, wound, and/or hand washing technique education [5] Sanitation: Disinfecting common surfaces with an EPA approved agent [6] Periodically testing wound cultures to gauge the prevalence of S. aureus/MRSA in the population or skin inspections for potential infections.

Appendix C Literature snapshot of hygiene practices effectiveness toward infection prevention

	CHXD			Hand or personal hygiene			Hygiene education			Sanitation		
Study type[4]	C	H	O	C	H	O	C	H	O	C	H	O
SR/MA		1	SSI	2		GI,RI	1		GI, RI		3	HAI,MRSA, SA, VRE
RCT	1	2	SSTI,MRSA	3		GI,RI						
Non-RCT (Quasi)		1	VRE									
Cohort												
Case Control												
CEA												
Other	3	1	MRSA,HAI	4	3	MRSA,GI,RI	2	1	SSTI, GI, RI	1	3	CD, MRSA,VRE,

Note: Number in the columns represents the number of studies that were found in the specified category. 1 CHXD: Chlorhexidine wash or wipes; hand or personal hygiene: use of soap and water, antibacterial soap, or hand sanitizer, limit personal item sharing, etc.; hygiene education: appropriate hand washing technique and/or identification of infection; sanitation: disinfection of high-touch surfaces 2 C: Community or H: Hospital intervention location; 3 O: Outcome; CD: Clostridium difficile, GI: gastrointestinal illness, HAI: hospital-acquired Infection, MRSA: Methicillin Resistant-SA, RI: respiratory illness, SA: Staphylococcus aureus, SSI: surgical site infection, SSTI: skin and soft tissue infection, VRE: Vancomycin-Resistant Enterococcus 4 Study type: SR/MA: Systematic Review/Meta-analyses; RCT: Randomized Controlled Trial (RCT); Non- RCT can be quasi-experimental; Cohort: prospective/retrospective; CEA: Cost-effectiveness analysis; Other: pre-post-test design, outbreak investigations where control measures were implemented or non-systematic reviews.

Appendix D Study population flowchart


Study Population
Active Duty Component Service members with a record available in the Defense Eligibility and Enrollment Reporting System (DEERs)
Active Duty
Recruit Training Population
Active Duty Component Service members stationed at one of nine recruit training facilities (Fort Benning, Fort Jackson, Fort Knox, Fort Leonard Wood, Fort Sill, Parris Island, San Dieago, Great Lakes, and Lackland) who can receive care at a Medical Treatment Facility (MTF) or
Active Duty Army
Recruit Training Population
Active Duty Component Service members with a record available in the Defense Eligibility and Enrollment Reporting System (DEERs) assigned to one of the Army's five recruit training facilities who can receive care at an MTF or Clinic
Active Duty Army
Trainee
Trainees are service members with a UIC code indicative of training at one of the five recruit training facilities (see spreadsheet for UIC codes).
Active Duty Army
Non-Trainee
Non-trainees are permanent party personnel with a UIC code (available in DEERs) indicative of non-training at one of the five recruit training facilities (see spreadsheet for UIC codes).

Appendix E 2009 ICD-9-CM Codes of interest

2009 ICD-9-CM Diagnosis Code 680
Carbuncle and furuncle
2009 ICD-9-CM Diagnosis Code 680.0
Carbuncle and furuncle of face
2009 ICD-9-CM Diagnosis Code 680.1
Carbuncle and furuncle of neck
2009 ICD-9-CM Diagnosis Code 680.2
Carbuncle and furuncle of trunk
2009 ICD-9-CM Diagnosis Code 680.3
Carbuncle and furuncle of upper arm and forearm
2009 ICD-9-CM Diagnosis Code 680.4
Carbuncle and furuncle of hand
2009 ICD-9-CM Diagnosis Code 680.5
Carbuncle and furuncle of buttock
2009 ICD-9-CM Diagnosis Code 680.6
Carbuncle and furuncle of leg except foot
2009 ICD-9-CM Diagnosis Code 680.7
Carbuncle and furuncle of foot
2009 ICD-9-CM Diagnosis Code 680.8
Carbuncle and furuncle of other specified sites
2009 ICD-9-CM Diagnosis Code 680.9
Carbuncle and furuncle of unspecified site
2009 ICD-9-CM Diagnosis Code 681
Cellulitis and abscess of finger and toe
2009 ICD-9-CM Diagnosis Code 681.0
Cellulitis and abscess of finger
2009 ICD-9-CM Diagnosis Code 681.00
Unspecified cellulitis and abscess of finger
2009 ICD-9-CM Diagnosis Code 681.01
Felon
2009 ICD-9-CM Diagnosis Code 681.02
Onychia and paronychia of finger
2009 ICD-9-CM Diagnosis Code 681.1
Cellulitis and abscess of toe
2009 ICD-9-CM Diagnosis Code 681.10
Unspecified cellulitis and abscess of toe
2009 ICD-9-CM Diagnosis Code 681.11
Onychia and paronychia of toe
2009 ICD-9-CM Diagnosis Code 681.9
Cellulitis and abscess of unspecified digit

2009 ICD-9-CM Diagnosis Code 682
Other cellulitis and abscess
2009 ICD-9-CM Diagnosis Code 682.0
Cellulitis and abscess of face
2009 ICD-9-CM Diagnosis Code 682.1
Cellulitis and abscess of neck
2009 ICD-9-CM Diagnosis Code 682.2
Cellulitis and abscess of trunk
2009 ICD-9-CM Diagnosis Code 682.3
Cellulitis and abscess of upper arm and forearm
2009 ICD-9-CM Diagnosis Code 682.4
Cellulitis and abscess of hand except fingers and thumb
2009 ICD-9-CM Diagnosis Code 682.5
Cellulitis and abscess of buttock
2009 ICD-9-CM Diagnosis Code 682.6
Cellulitis and abscess of leg except foot
2009 ICD-9-CM Diagnosis Code 682.7
Cellulitis and abscess of foot except toes
2009 ICD-9-CM Diagnosis Code 682.8
Cellulitis and abscess of other specified sites
2009 ICD-9-CM Diagnosis Code 682.9
Cellulitis and abscess of unspecified sites

2009 ICD-9-CM Diagnosis Code 683
Acute lymphadenitis

2009 ICD-9-CM Diagnosis Code 684
Impetigo

2009 ICD-9-CM Diagnosis Code 685
Pilonidal cyst
2009 ICD-9-CM Diagnosis Code 685.0
Pilonidal cyst with abscess
2009 ICD-9-CM Diagnosis Code 685.1
Pilonidal cyst without abscess

2009 ICD-9-CM Diagnosis Code 686
Other local infections of skin and subcutaneous tissue
2009 ICD-9-CM Diagnosis Code 686.0
Pyoderma
2009 ICD-9-CM Diagnosis Code 686.00
Pyoderma unspecified

2009 ICD-9-CM Diagnosis Code 686.8
Other specified local infections of skin and subcutaneous tissue

Appendix F Lost time in training calculations and assumptions

1. Rate calculations

Numerator=1 or more infections per trainee (count)
Denominator=Person-time in training (maximum 105 days)/105 training days
Multiplier=100 training-cycles

[Incident SSTI / (person-time/105 training days]*100 training-cycles

2. Lost-time in Training (LTT) calculation[22] and assumptions

$LTT = LT_{ct} + LT_{ht} + LT_{siqt} + LT_{wdlt} + LT_{ert} + LT_{rt}$

LT_{ct}=Total Lost time from a clinic visit
LT_{ht}=Total lost time from a hospital visit
LT_{siqt}=Total lost time from a quarters assignment
LT_{wdlt}=Total lost time from work duty limitations
LT_{ert}=Total lost time from an ER visit
LT_{rt}=Total lost time from being Recycled

- These calculations only consider those events which took place while in training. Training lasts for approximately 105 days.
- The difference between the date of event and the date of entry into training was calculated (called time to event). If the time to event was less than or equal to 105 days, the event was included in the analysis.
- This model includes a factor for being recycled. Persons with greater than seven days absence from training were considered to be recycled back into training; therefore, the total number of days lost would be 105 days since training was not completed.

(1) Clinic visit lost time (LT_{ct}) = Incidence of Clinic Visits (I_c) X Number of Clinic Visits per SSTI (N_s) X (Time in Days for Clinic Visit Appointment (0.5))

(2) Hospital stay lost-time (LT_{ht}) = Incidence of Hospitalization for SSTI (I_h) X Hospital Stay Duration (H_d)

- Accounts for being recycled back into training (105 days).
- If trainee has a length of stay of 4 days or greater in the hospital for SSTI assume recycled.

(3) Quarters assignment lost-time (LT_{siqt}) = Incidence of Clinic Visits (I_c) X Incidence for Quarters Assignment (1) X Days assigned to Quarters (3)

- On average SIQ is three days.

(4) Limited duty lost time (LT_{wldt}) = Incidence of Clinic Visits (I_c) X Incidence for limited duty Assignment (1) X Days for Duration of limited duty (5) X (30% work productivity reduction because of SSTI)

- On average days of limited duty for MRSA SSTI is five days
- Work productivity estimate is a literature based assumption

(5) ER lost time (LT_{wldt}) = Incidence of Clinic Visits (I_c) X Incidence for ER visit (1) X 0.50

(6) Recycled lost-time (LTrt) = LOS +30 days convalescent leave+21 days for remedial training (13; 114; 118; 144)

- A trainee whose length of stay is greater than or equal to 4 days in the hospital, they will be considered recycled.
- The definition of a recycle is "Any Soldier that is delayed in completion of training due to repeating certain phases of training. This includes personnel delayed for medical reasons, emergency leave, or other administrative reasons. MOS, ASI, or similar qualifications for which training is unchanged as a result of this action". (**AR 612–201 • 24 February 2011**)
- Trainees will not likely have to restart training entirely from the beginning; rather, the trainee will enter into a part of training that was missed. OSUT lasts 14 weeks is separated into five phases (red, white, blue, black, and gold). Each phase lasts approximately 3 weeks for each phase (21 days). We will assume that the trainee will lose 21 days.
- The natural break in OSUT is around week 6-7, additionally most SSTI occur during this time.
- Recycled time is considered in the hospital lost time in training variable so as to not double count time.

3. Example Generalized Linear Model [27]with negative binomial distribution and log-link function.

Lost time in training multivariate model dependent and independent variables

$[Y_i] = \text{Overall LTT for trainee (dependent vairable)}$
$E[Y_i] = \text{average LTT}$

$\text{Log } E[Y_i] = B_0 + B_1X_1 + B_2X_2 + B_3X_3 + B_3X_3$
$X_1 = \text{MRSA (yes or no)}; X_2 = \text{age}; X_3 = \text{Gender (male or female)}; X_4 =$ phase of training (1 or 2)

$\log [LTT] = \text{intercept} + b_1(\text{MRSA} = 1) + b(\text{age}) + B_3(\text{gender} = 2) + B_4(\text{phase} = 2)$

LTT=exp (intercept+ b_1 (MRSA=1)+ b_2 (age) + b_3 (sex=2) + b_4 (phase=2)) =

exp(intercept)*exp(b_1 (MRSA=1))*exp(b_2 (age))*exp(b_3 (sex=2))* exp(b_4 (phase=2))

Appendix G Cost calculations and parameters(1; 34)

Direct medical costs

1. Clinic costs

$\mathbf{C_c = I_c \times N_v \times C_{ac}}$

Variable	Variable name	Type of variable	Source of information
1. C_c	Clinic costs		
a. I_c	Incidence of clinic visits	Continuous	M2
b. N_c	Number of clinic visits	Continuous	M2
c. C_{ac}	Average cost for a clinic visit	Continuous	M2

2. Hospital costs

$\mathbf{C_h = I_h \times C_{as}}$

Variable	Variable name	Type of variable	Source of information
2. C_h	Hospital costs		
a. I_H	Incidence of hospitalization for SSTI	Continuous	M2
b. Cas	Average costs for a hospital stay	Continuous	M2

3. ER costs

$\mathbf{C_{er} = I_{er} \times C_{ae}}$

Variable	Variable name	Type of variable	Source of information
2. Cer	ER costs		
a. I_{er}	Incidence of ER visit for SSTI	Continuous	M2
b. C_{ae}	Average costs for a hospital stay	Continuous	M2

Indirect costs

3. Lost time in training (LTT) costs- cost variable (C_{LTT})

$\mathbf{C_{LTT} = C_{CLTT} + C_{HLTT} + C_{QLTT} + C_{LDLTT} + C_{RLTT}}$

Lost time in training (LTT) costs include 5 main elements lost time for clinic visits, hospital visits, assignment to quarters, work duty limitations, and recycling. Each

variable encompasses a trainee's salary, incidence for infection, a time factor (such as length of stay or days assigned to quarters) and incidence.

Variable	Variable name	Type of variable	Source of information
1. C_{CLTT}	**Clinic LTT (Sx I_cxN_c xT_c) costs**		
a. S	Average salaray/day/grade	Constant	M2[1], AMCOS[2]
b. I_c	Incidence of clinic visits	Continuous	M2
c. N_c	Number of clinic visits	Continuous	M2
d. T_c	Time in days for a clinic visit	Variable (0.5 days)	Reference(1; 34) model assumptions
2. C_{HLTT}	**Hospital LTT (Sx I_H xT_h) costs**		
a. S	Average salary/day/grade	Constant	M2, AMCOS
b. I_H	Incidence of hospitalization for SSTI	Continuous	M2
c. T_H	Hospital stay duration	Continuous	M2
3. C_{QLTT}	**Quarters LTT (Sx I_CxI_Q xT_Q) costs**		
a. S	Average salary/day/grade	Constant	M2, AMCOS
b. I_C	Incidence of clinic visit for SSTI	Continuous	M2
c. I_Q	Incidence of quarters assignment for SSTI	Continuous	M2
d. T_Q	Days assigned for quarters assignment	Variable (2-5 days)	Reference(1; 34), model assumption
4. C_{LDLTT}	**Limited Duty LTT (Sx I_Cx I_{LD} xT_{LD} xW_{LP}) Costs**		
a. S	Average salary/day/grade	Constant	M2, AMCOS
b. I_C	Incidence of clinic visit	Continuous	M2
c. I_{LD}	Incidence of limited duty	Continuous	M2
d. T_{LD}	Days of limited duty	Variable (2-5 days)	Reference(1; 34), model assumption
e. W_{LP}	Work productivity lost because of SSTI	Variable (15-30%)	Reference(1; 34), model assumption
5. R_{LTT}	**Recycled LTT (Sx I_Rx xT_R) Costs**		
a. S	Average salary/day/grade	Constant	M2, AMCOS
b. I_R	Incidence of recycle	Continuous	M2
d. T_R	Days lost to recycle	Continuous	M2

[1] Military Health Systems Mart (M2)-provides both disease and cost information
[2] Army Military-Civilian Cost Center (AMCOS)

4. Total Costs (TC) for overall and MRSA SSTI

TC= Cc+Ch+Cer+Cltt

4.TC	**Total Costs**		
a. Cc	Total Clinic Visit Costs	Continuous	Model Calculation
b. Ch	Total Hospital Visit Costs	Continuous	Model Calculation
c. Cer	Total ER visit Costs	Continuous	Model Calculation
c. Cltt	Total Lost Time in Training Costs	Continuous	Model Calculation

Cost calculation assumptions

1. Lost productivity estimates and calculations are based on information provided from the CAM; therefore, the assumptions used to generate the estimate in the CAM will be applied to this analysis as well. The assumptions are listed below(1).

i. Clinic visit time: Estimated average time (travel from place of duty to clinic, wait at clinic and be seen by medical practitioner travel from clinic to place of duty (approximately 2 hours)(1).

ii. Although the CAM approximates limited duty duration of 15 days if data are unavailable, this study will use a shorter duration. This assumption will be changed to reflect LDD of a trainee population which was estimated as an average of 5 days ± 4 days in a previous study (144).

iii. If data are unavailable, quarters assignment will be approximated as 2 days with the max of 3 days allowed. According to references stated in the CAM technical report, physicians should use quarters if the individual could return within 72 hours(1).

iv. Cost calculations will have to incorporate an adjustment factor for inflation, time in training, and the number of follow-up visits.

Appendix H Exclusion log

Exclusion log[a]

Author	Journal Name/Year	Main intervention	Reason for exclusion[1]

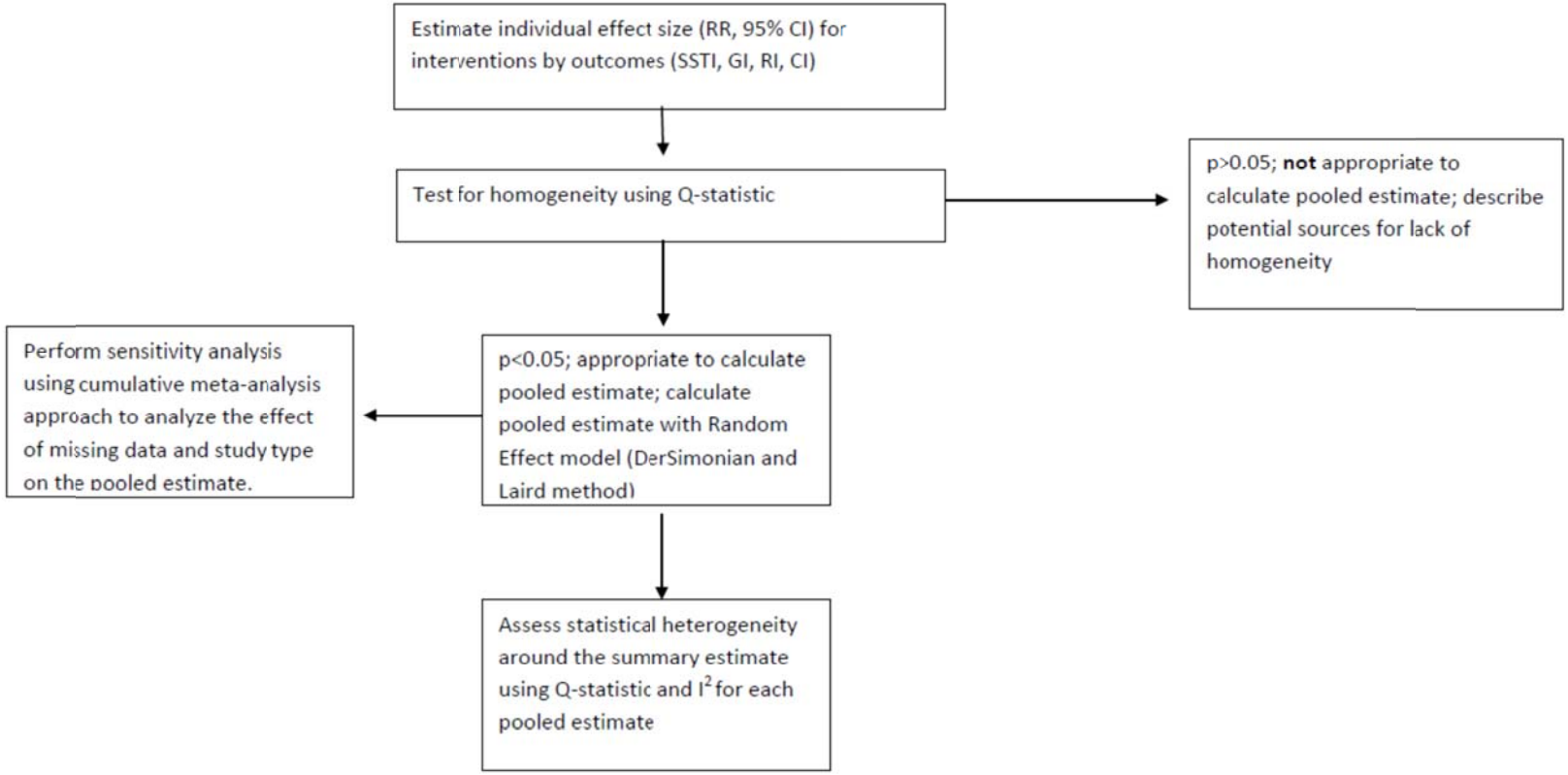
[a]Acceptable terms for reasons for exclusion: Cases series or report; review, letter or editorial; not enough information-estimates not provided, outcome not specified, intervention not specified; did not fit inclusion criteria; language other than English; poor rating

Appendix I Summary table for included studies

Source information	
Study duration (dates)	
Country	
Methods	
Design	
Participants	
Setting	
Location	
Intervention	
Outcomes	
Risk of bias	
Major sources of confounding or bias	
Other	
Authors conclusions	
Assessment of author's conclusions	
Notes	

Note: Summary tables will not include all variables when reported.

Appendix J Systematic review statistical analysis flowchart


Estimate individual effect size (RR, 95% CI) for interventions by outcomes (SSTI, GI, RI, CI)
Test for homogeneity using Q-statistic
p>0.05; **not** appropriate to calculate pooled estimate; describe potential sources for lack of homogeneity
p<0.05; appropriate to calculate pooled estimate; calculate pooled estimate with Random Effect model (DerSimonian and Laird method)
Perform sensitivity analysis using cumulative meta-analysis approach to analyze the effect of missing data and study type on the pooled estimate.
Assess statistical heterogeneity around the summary estimate using Q-statistic and I^2 for each pooled estimate

Appendix K Cost effectiveness calculations and parameters

Cost effectiveness outcome calculations

C=Cost
E=Effectiveness

Example calculations:

- Average CER for hand hygiene strategy= $C_{\text{Hand Hygiene}}/E_{\text{hand hygiene}}$
- Average CER for community-education strategy= $C_{\text{community-education}}/E_{\text{community-education}}$

IC=Incremental costs= TC_1- TC_3 or TC_2- TC_3
IE= Incremental health outcome= E_1- E_3 or E_2- E_3

TC_1=Total costs in present terms of prevention strategy 3=Direct medical costs + Direct Nonmedical Costs + Indirect costs
TC_2=Total costs in present terms of prevention strategy 2=Direct medical costs + Direct Nonmedical Costs + Indirect costs
TC_3=Total costs in present terms of prevention strategy 1=Direct medical costs + Direct Nonmedical Costs + Indirect costs

E_1=Total health outcome for prevention strategy 3
E_2=Total health outcome for prevention strategy 2
E_3=Total health outcome for prevention strategy 1

C/E=Cost effectiveness ratio=IC/IE

FB MRSA study Case Report Form (CRF) variables

	Variable	Measure	Source
Clinical encounter	ICD-9 codes[1]	Categorical	FB MRSA Study CRF
	Clinical diagnosis	Categorical	FB MRSA Study CRF
	Resolution	Categorical	FB MRSA Study CRF
	Complication	Categorical	FB MRSA Study CRF
	Physical profile	Categorical/number of days	FB MRSA Study CRF
Procedure	Incision and Drainage	Categorical	FB MRSA Study CRF
	Wound Culture	Categorical	FB MRSA Study CRF
	Antibiotics prescribed	Categorical	FB MRSA Study CRF
	Follow-up visit	Categorical/number of days	FB MRSA Study CRF
Hospitalization	Outcome	Categorical	FB MRSA Study CRF
	Discharge diagnosis	Categorical	FB MRSA Study CRF
	Intensive care	Categorical	FB MRSA Study CRF
	Length of stay	Number of days	FB MRSA Study CRF

Variables from Objectives 1-3

	Variable	**Measure**	**Source**
Clinical encounter	ICD-9 codes[1]	Categorical	Objective 1
	Clinical diagnosis	Categorical	Objective 1
	Resolution	Categorical	Objective 1
	Complication	Categorical	Objective 1
	Physical profile	Categorical/number of days	Objective 1
Procedure	Incision and Drainage	Categorical	Objective 1
	Wound Culture	Categorical	Objective 1
	Antibiotics prescribed	Categorical	Objective 1
	Follow-up visit	Categorical, number	Objective 1
Hospitalization	Outcome	Categorical	Objective 1
	Discharge diagnosis	Categorical	Objective 1
	Intensive care	Categorical	Objective 1
	Length of stay	Number of days	Objective 1

Health outcome measures and effects and sources

Variable	**Measure**	**Source**
Incidence of SSTI	number	FB MRSA Study, objective 1
Incidence of MRSA-SSTI	number	FB MRSA Study, objective 1
Prevalence of *S. aureus*	proportion	FB MRSA Study, objective 1
Probability of developing 1 or more SSTI	rate	FB MRSA Study, objective 1
Probability of developing 1 or more MRSA-SSTI	rate	FB MRSA Study, objective 1
Probability of developing a complication	rate	FB MRSA study, objective 1-2
Probability of being hospitalized	rate	FB MRSA Study, objective 1
Probability of being dismissed from training	rate	FB MRSA Study
Probability of SSTI prevented by existing practice	Relative risk (odds ratio)	Published literature, Objective 3
Probability of SSTI prevented by basic approach	Relative risk (odds ratio)	FB MRSA Study, objective 3
Probability of SSTI prevented by enhanced standard	Relative risk (odds ratio)	FB MRSA Study, objective 3
Probability of SSTI prevented by enhanced standard plus Chlorhexidine	Relative risk (odds ratio)	FB MRSA Study, objective 3
Probability of MRSA-SSTI prevented by existing practice	Relative risk (odds ratio)	Published literature, Objective 3
Probability of MRSA-SSTI prevented by basic approach	Relative risk (odds ratio)	FB MRSA Study, objective 3
Probability of MRSA-SSTI prevented by enhanced standard	Relative risk (odds ratio)	FB MRSA Study, objective 3
Probability of MRSA-SSTI prevented by enhanced standard plus Chlorhexidine	Relative risk (odds ratio)	FB MRSA Study, objective 3

Cost estimate variables and sources

Variable	Measure	Estimate Source
Prevention program costs		
Basic approach (preventive medicine brief and standardized care at SSTI clinic)	US Dollars($)	FB MRSA Study
Enhanced Standard (education and surveillance, standardized care at SSTI clinic))	US Dollars($)	Published literature, FB MRSA Study
Enhanced Standard plus weekly chlorhexidine wash	US Dollars($)	Published literature, FB MRSA Study
Direct medical costs (Outpatient and Inpatient)		
Treatment by medical personnel	US Dollars($)	Objective 2, TRICARE
Clinical care (I&D), wound culture	US Dollars($)	Objective 2, TRICARE
Antibiotic prescriptions	US Dollars($)	Objective 2, TRICARE
Laboratory procedures (e.g. laboratory analysis, microbiology, etc.)	US Dollars($)	Objective 2, TRICARE
Follow-up visits	US Dollars($)	Objective 2, TRICARE
Isolation measures	US Dollars($)	Objective 2, TRICARE
Hospital admission	US Dollars($)	Objective 2, TRICARE
Emergency room visit	US Dollars($)	Objective 2, TRICARE
Direct non-medical costs (Lost-time)		
Patient visit time	Time in days for clinic visit appointment (US Dollars $)	Published literature, Army cost avoidance model, FB MRSA Study
Physical profile (limited duty days or sick in quarters)	US Dollars($)	Objective 2; Army cost avoidance model, FB MRSA study
Indirect costs		
Lost earnings from inability to complete training (attrition or medical discharge attributed to infection).	Average salary per day per pay grade (US Dollars $)	Published literature, Army Manpower Cost System (AMCOS)

Appendix L Search Strategy Terms

Search strategy, including time period included in the synthesis and keywords

- 1.1. Time period from 1980 through 2014
- 1.2. Keywords groups by category-outcome and prevention method
  - 1.2.1. Intervention
    - 1.2.1.1. Anti-infective agent such as triclosan, chlorhexidine and alcohol based agents
    - 1.2.1.2. Infection control to include skin care, hand washing or hygiene
    - 1.2.1.3. Education to include hygiene methods and practices as well as use of lectures and posters.
  - 1.2.2. Outcome included respiratory, gastrointestinal, and SSTI illness
    - 1.2.2.1. Skin infection
      - 1.2.2.1.1. Cellulitis
      - 1.2.2.1.2. Abscess
      - 1.2.2.1.3. Impetigo
      - 1.2.2.1.4. Streptococc*
      - 1.2.2.1.5. Staphylococcal skin infection
      - 1.2.2.1.6. Skin disease
    - 1.2.2.2. Gastrointestinal illness
      - 1.2.2.2.1. Vomiting
      - 1.2.2.2.2. Diarrhea
    - 1.2.2.3. Respiratory infection
      - 1.2.2.3.1. Influenza like illness (ILI)
      - 1.2.2.3.2. Febrile respiratory illness (FRI)
      - 1.2.2.3.3. Acute respiratory illness (ARI)
    - 1.2.2.4. Community acquired infection (CAI)
      - 1.2.2.4.1. Community-acquired infection
      - 1.2.2.4.2. Staphylococcus
      - 1.2.2.4.3. Streptococcus
      - 1.2.2.4.4. Pneumonia
  - 1.2.3. Method of application
    - 1.2.3.1. Shower
    - 1.2.3.2. Bath
    - 1.2.3.3. Wash
    - 1.2.3.4. Clean
    - 1.2.3.5. Sanitize
    - 1.2.3.6. Cleanser
  - 1.2.4. Study design
    - 1.2.4.1. Prevention
    - 1.2.4.2. Intervention
    - 1.2.4.3. Health intervention
    - 1.2.4.4. Program evaluation

Appendix M Inclusion and exclusion log definitions

Reasons

1. Intervention not of interest or no intervention was implemented
2. Outcome not of interest (i.e. secondary attack rate reported, but no information regarding primary infection)
3. Lack of data/information
4. Systematic review
5. Duplicate
6. Language other than English

Study type

Randomized controlled trial (RCT)
Double-blind (DB)-RCT
Cluster (C)-RCT
non-RCT
Pre-post/quasi experimental (QE)
Prospective cohort (PC)
Retrospective cohort (RC)
Case control (C-C)
Cross-sectional (CS)
Systematic review (SR)
Literature review (LR)
Outbreak investigation (OI)

Outcomes

Communicable/infectious illness (CI/II)
Respiratory illness (RI)
Gastrointestinal illness (GI)
Skin infection (SI)

Appendix N Excluded Studies

			Intervention/prevention program	Outcomes				Reason	
Author	Year	Journal		CI/I	RI	GI	SI		
Feacham	1984	Bulletin of the World Health Organization	Personal and domestic hygiene education			x		4	
Clemens	1987	American Journal of Epidemiology	Water sanitation behavior education			x		1	
Sircar	1987	Journal of Diarrhoeal Disease Research	Hand washing			x		3	
Bartlett	1988	American Journal of Epidemiology	Infection control and child hygine education			x		1	
Farr	1988	American Journal of Epidemiology	Virucidal nasal tissues		x			1	
Longini	1988	American Journal of Epidemiology	Virucidal nasal tissues		x			1	
Stergachis	1990	Journal of General Internal Medicine	Self-care pamphlet		x			1	
Lee	1991	Southeast Asian J Trop Med Public Health	Community outreach			x		1	
Caldwell	1995	Journal of Oklahoma State Medical Association	Infection control measures			x		3	
Mohle-Boetani	1995	American Journal of Public Health	Infection control measures			x		3	
Gorter	1998	International journal of epidemiology	Hygiene behavior/practices observed			x		1	
St Stauvier	1998	Public health reports	Hygiene behavior survey		x	x		1	
Barros	1999	Acta Paediatrica	Hygiene behavior observed		x			1	
Ladegaard	1999	Ugeskrift for laeger	Hand Hygiene Program	x				6	
Moe	2001	Journal of American College Health	None			x		1	
Gibson	2002	Journal of Applied Microbiology Symposium Supplement	Handwashing with antibacterial soaps			x		2,4	
Rodriguez	2002	Journal of School Nursing	Handwashing	x				4	
Curtis, V.	2003	The Lancet, infectious diseases	Handwashing			x		4	

Campbell	2004	Journal of Clinical Microbiology	Decolonization with mupirocin, bath with antimicrobial skin cleanser, disinfect barracks with 5% bleach solution				x	3
Lau	2004	Emerging infectious Diseases	Hygiene behavior/risk factor survey		x			1
Meadows	2004	BMC Public Health	Hand sanitizer	x				4
Turner	2004	Antimicrobial Agents and Chemotherapy	Hand cleanser		x			1,2
CDC-MMWR	2005	MMWR	None				x	1
Lee, G.	2005	Pediatrics	Hygiene behavior/practices survey		x	x		1,2
Lee, T.	2005	American Journal of Preventive Medicine	Non-vaccine interventions-personal, administrative, and engineering controls		x			4
Nguyen	2005	Emerging infectious Diseases	Outbreak control measures (daily hexachlorphene showers, disinfection of facility surfaces, hand-hygiene education)				x	3
White	2005	Journal of American College Health						5
Dubois	2006	Epidemiology and Infection	Hygiene behavior/risk factor survey			x		2
Rabie	2006	Tropical Medicine and International Health	Handwashing		x			4
Rosen	2006	Preventive Medicine	Hand hygiene education and compliance	x				3
Turabelidze	2006	Emerging infectious Diseases	Hygiene behavior/practices survey				X	1
Bloomfield	2007	American Journal of Infection Control	Hand washing and hand sanitizers		x	x	x	4
Coronado	2007	Epidemiology and Infection	Hygiene behavior/risk factor survey				x	1,3
Ellis	2007	Antimicrobial Agents and Chemotherapy	Nasal decolonization with mupirocin among soldiers				x	1
Kotch	2007	Pediatrics	Hygiene program+hand washing ewupment			x		1
Larson	2007	Public health nursing	Hygine, education, and OTCs		x			4
Wiese	2007	Clinical Infectious Diseases	Decolonization with mupirocin, antibacterial hand sanitizer, octenidin-based wash solution, gargle with chlorhexidine solultion, disinfection of personal items and surfaces				x	3
Aiello	2008	American Journal of Public Health	Hand-hygiene interventions		x	x		4

Archibald	2008	Infection Control and Hospital Epidemiology	Infection control measures (disinfection and personal hygiene)				x	3
Cowling	2008	PLOS one	Hand hygine (soap and hand sanitizer)		X			2
Ejmot	2008	The Cochrane Collaboration	Hand washing			x		4
Lennell	2008	ACTA Paediatrica	Hand hygiene (soap and sanitizer)	x				2,3
McDonald	2008	BMC Public Health	Personal and domestic hygiene education			x		4
Neri	2008	Journal of Travel Medicine	Hygiene behavior/practices survey			x		1
Cowling	2009	Annals of internal medicine	Education, face masks, hand hygiene		x			2,5
Deger	2009	Journal of Correctional Health Care	Infection control (daily showering, washing hands, covering wounds, not sharing personal items)				x	3
Heijne	2009	Emerging infectious Diseases	Personal and domestic hygiene education			x		2
Jefferson	2009	The Cochrane Collaboration	Physical interventions		x			4
Thumma	2009	American Journal of Infection Control	Hygiene behavior/practices survey		x	x		1
Tillett	2009	British Journal of Sports Medicine	Prevention guidelines, education, pocket alcohol hand gel			x		3
Harris	2010	Journal of Hospital Infection	Infection control measures			x		4
Lee	2010	Journal of School Health	Infection control measures			x		4
Leggat	2007	Travel Medicine and Infectious Disease	Disease transmission and prevention knowledge survey		x			1
Maree	2010	Clinical Infectious Diseases	No intervention implemented				x	1
McKenzie	2010	Trials	Study protocol for hand hygine program w/ hand sanitizer use & educational components	x				3
Oller	2010	Journal of Athletic Training	Infection control meaures and education				*x*	2
Mitchell	2011	Clinical Infectious Diseases	Hygiene behavior/practices survey		x			1,2
Fritz	2012	Journal of School Nursing	Hygiene behavior/practices survey				x	3
Whitman	2013	Infection Control and Hospital Epidemiology	Chlorhexidine impregnated cloths				x	2
Agolory	2013	PLOS one	Hygiene behavior/practices survey		x			1,2
Pedersen	2013	The Iowa Orthopaedic Journal	Survey of hygiene policies and procedures				x	1,2
Dreibebis	2014	American Journal of Public Health	Hygiene promotion and water treatment			x		1

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